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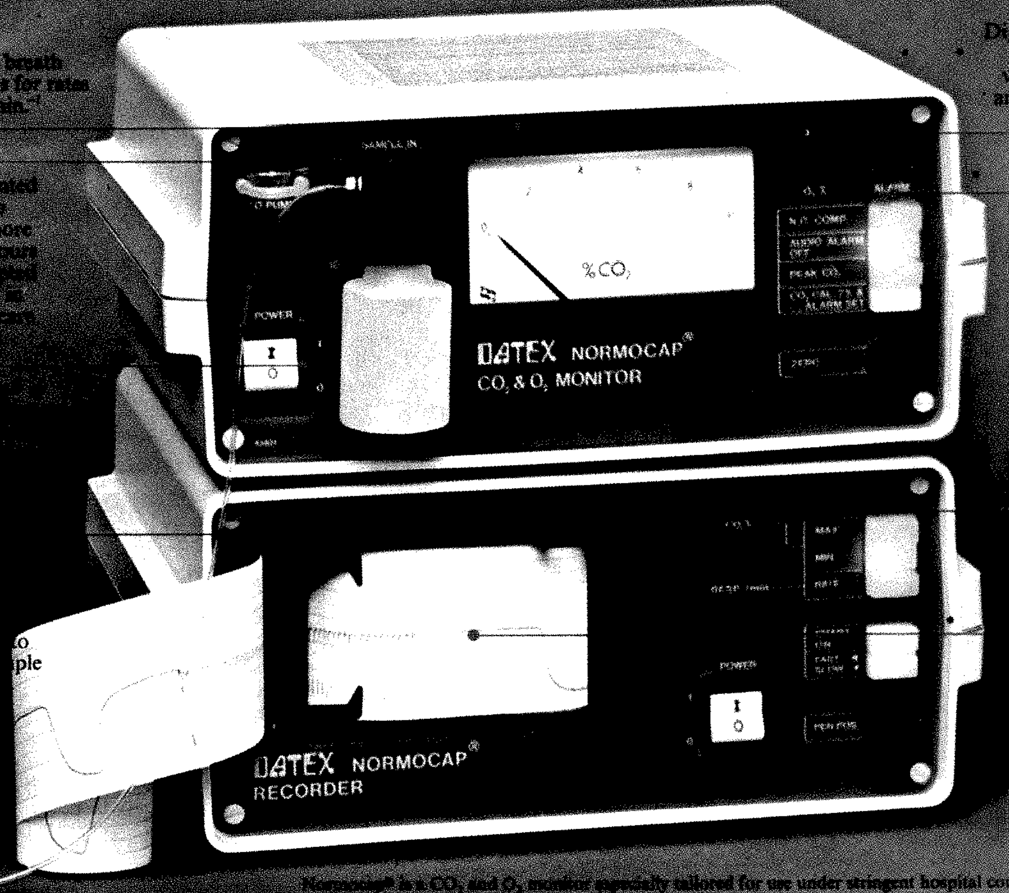

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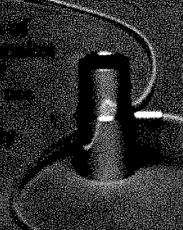

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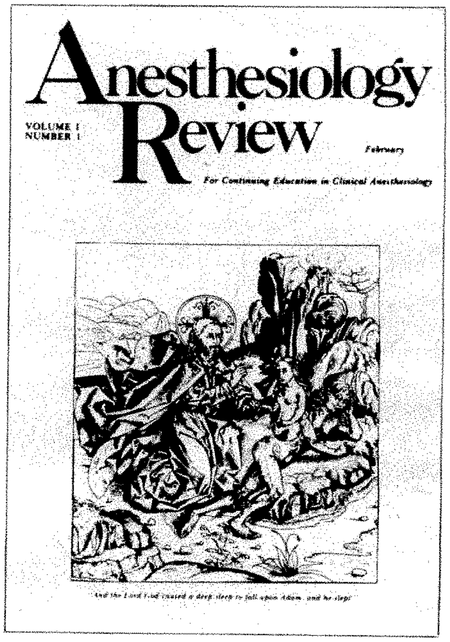
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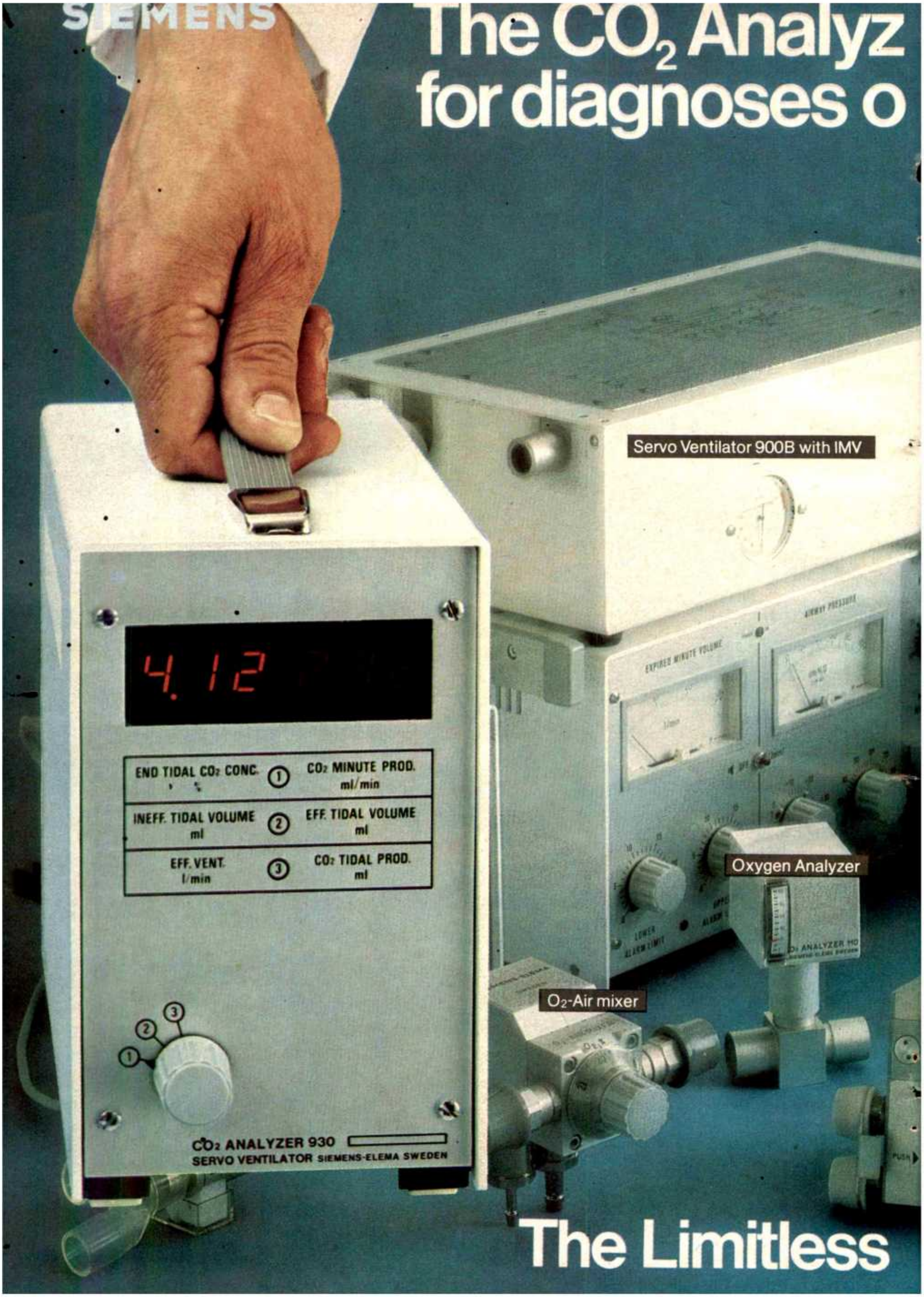

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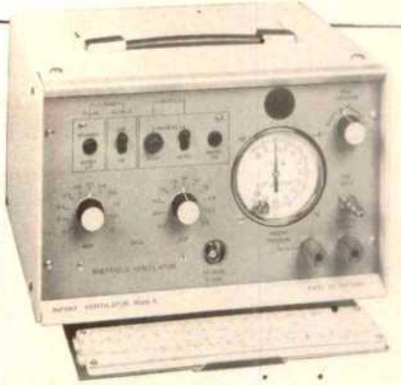

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Contra-indications Respiratory depression; obstructive airways disease. Concurrent administration with MAOIs or within 2 weeks of discontinuation of them.

Warnings A transient fall in blood pressure may occur after i.v. administration of Sublimaze*.

Side effects/Overdosage Doses over 200µg cause significant respiratory depression; reversed by naloxone 0.1-0.2mg. Bradycardia may be antagonised by atropine; muscular rigidity by muscle relaxants. An additive effect may be seen with concomitant use of other narcotics or CNS depressant drugs. Nausea, vomiting, tolerance and dependence may occur.

Precautions Myasthenia gravis. Reduce dosage in the elderly, hypothyroidism and chronic hepatic disease. Use in labour may cause respiratory depression in the neonate

Pregnancy Little human evidence, no adverse animal effects.

Legal category POM MDA

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Package quantities Sublimaze* is supplied in 2 ml or 10 ml ampoules in packs of 10. Each ml contains 0.05mg fentanyl.

Basic NHS cost 2 ml × 10 £4.13. 10 ml × 10 £17.03.

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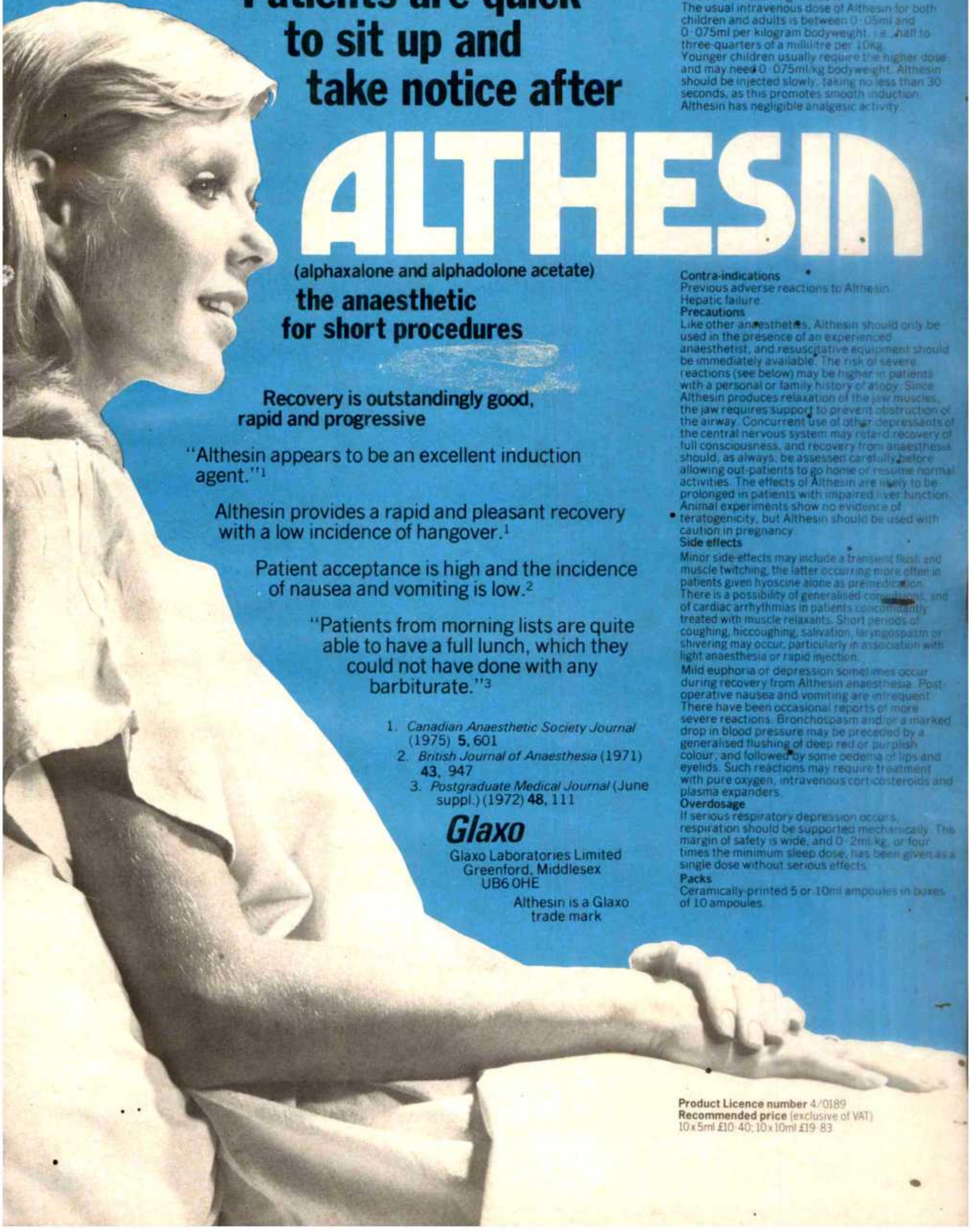

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1. *Canadian Anaesthetic Society Journal* (1975) **5**, 601
2. *British Journal of Anaesthesia* (1971) **43**, 947
3. *Postgraduate Medical Journal* (June suppl.) (1972) **48**, 111

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Uses

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The usual intravenous dose of Althesin for both children and adults is between 0·05ml and 0·075ml per kilogram bodyweight, i.e. half to three-quarters of a millilitre per 10kg.
Younger children usually require the higher dose and may need 0·075ml/kg bodyweight. Althesin should be injected slowly, taking no less than 30 seconds, as this promotes smooth induction.
Althesin has negligible analgesic activity.

Contra-indications

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Hepatic failure.

Precautions

Like other anaesthetics, Althesin should only be used in the presence of an experienced anaesthetist, and resuscitative equipment should be immediately available. The risk of severe reactions (see below) may be higher in patients with a personal or family history of atopy. Since Althesin produces relaxation of the jaw muscles, the jaw requires support to prevent obstruction of the airway. Concurrent use of other depressants of the central nervous system may retard recovery of full consciousness, and recovery from anaesthesia should, as always, be assessed carefully before allowing out-patients to go home or resume normal activities. The effects of Althesin are likely to be prolonged in patients with impaired liver function. Animal experiments show no evidence of teratogenicity, but Althesin should be used with caution in pregnancy.

Side effects

Minor side-effects may include a transient flush and muscle twitching, the latter occurring more often in patients given hyoscine alone as premedication. There is a possibility of generalised convulsions, and of cardiac arrhythmias in patients concomitantly treated with muscle relaxants. Short periods of coughing, hiccoughing, salivation, laryngospasm or shivering may occur, particularly in association with light anaesthesia or rapid injection.

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1980	
December 11 8.15 pm	Dr J. C. Frankland: “Cavemen, Spacemen and Von Daniken's Gold.”
1981	
January 15 8.15 pm	Gp Capt. A. J. Merrifield: “Anaesthesia and the Defence Medical Services.”
February 12 8.15 pm	Registrar's Papers for ICI Anaesthetic Registrar's Prize and Abbott Prize.
March 12 8.15 pm	Dr R. Greenbaum: “Some Aspects of Brain Protection.” (To be held at Preston Postgraduate Centre)
April 10 8 pm	Joint meeting with the Liverpool Society of Anaesthetists, to be held in Liverpool at the Liverpool Medical Institution. Professor J. E. Utting, Dr P. E. Penna.

The above meetings (unless otherwise indicated) will take place in the Stopford Building, University of Manchester, Oxord Road, Manchester M13 9PL. Those attending the meetings will assemble for coffee at 8 pm.

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Der Anaesthesist

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BRITISH JOURNAL OF ANAESTHESIA

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EDITORIAL

ANAESTHESIA, AWARENESS AND AUTOMATION

Forty-four years have elapsed since Gibbs, Gibbs and Lennox (1937) suggested that the then recently discovered technique of electroencephalography might be usefully applied during anaesthesia. During this time the effect of anaesthetic agents on the electrical activity of nervous tissue both in bulk and in the single cell have been extensively studied and faithfully recorded; we are edging closer to a full understanding of the mechanism of anaesthesia and as a research tool in these studies electroencephalography (e.e.g.) has played a major role. The changes in the e.e.g. during both inhalation and i.v. anaesthesia have been defined (for example Courtin, Bickford and Faulconer, 1950) but the usefulness of the e.e.g. as a monitor of the depth of anaesthesia has been limited by the cost of the apparatus and the complexity of the information output necessitating expert interpretation. In the last review in this journal of the methods available for the measurement of the depth of anaesthesia (Robson, 1969) it was concluded that "there is as yet no practical means of measurement of the depth of anaesthesia within the range required today". In the subsequent decade many studies have been made of methods of processing the e.e.g. to present the anaesthetist with the two pieces of information he requires. Is the patient unaware of his surroundings? Is the level of anaesthesia sufficient to enable surgery to take place?

During anaesthesia with volatile agents and spontaneous breathing the signs of Snow and Guedel remain pre-eminent in answering the two questions; e.e.g. monitoring for this purpose is gilding the lily. The use of muscle relaxants, however, may afford acceptable operating conditions while obtunding the classical signs of anaesthesia. Awareness has become a very real risk and receives increasing attention in the lay and medical press (Leading article, 1976, 1978); a legal test case is surely not far away. The addition of a suitable concentration of an inhalation agent to the inspired gases during controlled ventilation under muscle relaxation assures an amnesic state, at least. However, the increasing demand for pollution-free techniques, the attractions of total i.v. techniques and the unique requirements of obstetric anaesthesia are reasons for a move away from inhalation agents which, in any case, would be unnecessary if a reliable index of depth of anaesthesia existed. Most techniques of anaesthesia allow warning to the anaesthetist of a dangerously deep level of anaesthesia (corresponding to burst suppression and increasing electrical silence on e.e.g.); a simple, reliable and objective index of dangerously light anaesthesia remains elusive.

Two main types of recording of the electrical activity of the brain with scalp electrodes have been made in an attempt to define an index of anaesthesia: sensory evoked potentials and a processed form of the e.e.g. Evoked cortical and brain stem potentials offer the attraction of being easily obtained, recorded and analysed. The changes in amplitude and configuration caused by anaesthetic agents are well documented in both experimental animals and man (Angel, Berridge and Unwin, 1973); encouraging dose–response curves of parameters of the evoked response (e.g. normalized variance) against anaesthetic dose have been constructed (Horvath, 1969) and correlation of cardiovascular reflex responses with auditory evoked potentials during changes in depth of anaesthesia have been demonstrated (Linden et al., 1974). Despite these findings, no method of using changes in the latency or amplitude of sensory evoked responses as a reliable guide to depth of anaesthesia has evolved.

Processed derivatives of the e.e.g. have undergone more promising development. The cerebral function monitor (Prior, 1979) has proved to be extremely useful in detecting global ischaemia in anaesthesia and intensive care. Its usefulness as an indicator of anaesthetic depth is limited because the response is not consistent between different anaesthetic agents, there is a need for considerable experience and expertise on the part of the anaesthetist in the analysis of the data output and, as it relies for simplicity on a composite of the frequency and amplitude of the electrical activity between a single pair of electrodes, its ability to detect the subtle electrical changes (if they exist) between oblivion and awareness must be in doubt.

Other forms of e.e.g. processing appear to offer more encouraging results and form the basis of a recent review (Levy et al., 1980). Power-spectrum analysis forms an attractive method, retaining most of the information contained in the original e.e.g. Berezowskyj and others (1976), for example, claim an accurate estimation of the level of anaesthesia in 55–80% of their cases. Period-amplitude analysis (Davis and Klein, 1977) has also been used as an intraoperative monitoring aid, but remains experimental. An anterior shift of the dominant e.e.g. rhythm during anaesthesia was demonstrated by Tinker, Sharborough and Michenfelder (1977) in monkeys at a consistent proportion of MAC for each anaesthetic tested; these authors speculate that this e.e.g. change may signal loss of awareness and suggest that sustained anterior e.e.g. amplitude dominance may provide assurance of loss of awareness during anaesthesia.

All methods of e.e.g. processing have the disadvantage of expense (if commercially available) and of presenting data that are incomprehensible to the anaesthetist untrained in e.e.g. methods. This second problem ceases to exist if the anaesthetist is withdrawn from the feedback loop.

With our improved knowledge of pharmacokinetics (Allott, Steward and Mapleson, 1976) the time is surely near when the loop of servo-anaesthesia may be closed, with the partial or total exclusion of the anaesthetist from the regulatory process. Bickford (1950) and others described methods of servo-anaesthesia of the closed-loop type relying on the attainment of a threshold energy level of cerebral activity causing a predetermined quantity of anaesthetic to be delivered. Less rigid, adaptive techniques have been suggested subsequently which offer the anaesthetist advice which may be accepted or rejected (Chilcoat, 1973). In these examples interpretation of complex data ceases to be a problem.

One further method of detecting wakefulness during general anaesthesia has been devised which does not rely on the monitoring of electrical potentials. Tunstall (1977) described the isolated forearm technique in which evidence of awareness is provided by signals from the patient's hand spared from neuromuscular blockade by occlusion with a pneumatic tourniquet. For the first time it may now be possible to compare electrophysiological methods of gauging depth of anaesthesia with an objective confirmation of wakefulness.

David Saunders

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ERRATUM

EFFECTS OF ENFLURANE ON CARDIOVASCULAR FUNCTION

(*Br. J. Anaesth.*, **52**, 1087)

Throughout the text of this paper, and in figure 3, the index of myocardial contractility, d*p*/d*t* IIP, should have been expressed as a ratio, d*p*/d*t* : IIP.

Br. J. Anaesth. (1981), 53, 5

ANAESTHETIC REQUIREMENT IN MICE SELECTIVELY BRED FOR DIFFERENCES IN ETHANOL SENSITIVITY

D. D. KOBLIN AND J. E. DEADY

SUMMARY

Anaesthetic requirements for nitrous oxide, enflurane and isoflurane were determined in mice selectively bred for their susceptibility ("long-sleep" mice) or resistance ("short-sleep" mice) to alcohol. Nitrous oxide and enflurane requirements, measured by the rolling-response test, were 34 and 20% greater, respectively, in short-sleep mice than in long-sleep mice. Although isoflurane requirement was 39% greater when measured by the tail-clamp test, it was not significantly different when measured by the rolling-response test. The greater anaesthetic requirement for short-sleep mice was not associated with a different synaptic membrane phospholipid, fatty acid or cholesterol composition.

Through selective breeding, two lines of mice were produced: "long-sleep" and "short-sleep" mice, which differ in their ethanol-induced sleep times (McClearn and Kakihana, 1973). Short-sleep mice are more resistant to the hypnotic effect of alcohol. We determined whether this resistance to alcohol was associated with a greater requirement for general anaesthesia. We also determined whether any such cross-tolerance was associated with alterations in neuronal membrane lipid composition. Such an association might be anticipated because of the following: the excellent correlation between lipid solubility and anaesthetic potency (Eger et al., 1969; Miller et al., 1972); the suggested role of membrane lipids in controlling neuronal transmission (Trudell, 1977); the influence of lipid composition on the ability of general anaesthetics to perturb membranes (Miller and Pang, 1976; Pang and Miller, 1978).

METHODS

We studied female long-sleep (LS) and short-sleep (SS) mice selectively bred by the Institute for Behavioral Genetics, University of Colorado at Boulder, for their differences in ethanol-induced sleep time.

Nitrous oxide ED_{50} (the dose of nitrous oxide required to abolish the righting reflex in 50% of mice) was measured in a 20-litre hyperbaric chamber (Halsey et al., 1975). For each determination, as many as eight unrestrained mice were placed in individual wire mesh cages which could be rotated at 4 rev min^{-1} in the hyperbaric chamber. In two additional restrained mice, rectal temperatures were monitored and maintained between 36.5 and 38.0 °C by adjusting the chamber temperature with circulating water heat exchangers. Carbon dioxide was removed by circulating the chamber gases through a soda-lime container. After the chamber was flushed with 100% oxygen, nitrous oxide 1.22 atm was added. Mice were tested after a 30-min equilibration period. Animals that rolled over twice during five completed turns of the rotator were considered anaesthetized. Nitrous oxide was then added (usually in increments of 0.11 atm) to the chamber, and the righting reflex was again determined after a 15-min equilibration period. The nitrous oxide concentration was increased in 0.11-atm steps until all animals failed the rolling-response test. The concentrations were then decreased in steps until all animals could right themselves. Oxygen pressure was maintained between 0.6 and 1.0 atm.

Rolling response ED_{50} for isoflurane and enflurane were determined in a similar manner, except that a continuous flow of oxygen 4 litre min^{-1} and controlled amounts of isoflurane or enflurane, delivered from a temperature-compensated vaporizer, passed continuously through the chamber during the entire experimental period. An initial 1-h equilibration at an approximate concentration of 0.004 atm for isoflurane or 0.01 atm for enflurane was imposed before testing the righting reflex. Subsequent

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measurements were taken after incremental changes of isoflurane 0.0005 atm or enflurane 0.001 atm accompanied by 30 min of equilibration.

The anaesthetic potency of isoflurane was also determined by measuring the concentration of isoflurane required to abolish movement in response to a painful stimulus. Groups of eight mice were anaesthetized with isoflurane in oxygen 4 litre min^{-1} in individual Perspex chambers. Rectal temperatures were monitored in each mouse and maintained between 36.5 and 38.0 °C. Animals were initially exposed to isoflurane approximately 0.015 atm for 1 h. An alligator clip was then applied to the tail and oscillated for 60 s, during which time the mouse was observed for movement. Isoflurane concentration was then increased or decreased in 0.003-atm steps until the concentrations permitting and preventing movement were obtained for each animal.

Anaesthetic concentrations were measured by gas chromatography. Anaesthetic requirement (ED_{50}) was determined for each mouse by averaging the anaesthetic concentrations that just abolished or just allowed the righting reflex, or that just prevented and permitted movement in response to painful stimulation. The observer was unaware of the strain of the animals when measurements were taken. ED_{50} and standard error for a group of mice were calculated from the individual values, and statistical significance was calculated with an unpaired *t* test.

Mice were 8, 16 and 19 weeks old when tested for the rolling-response ED_{50} for nitrous oxide, isoflurane and enflurane; they were 22 weeks old when examined for the tail-clamp response to isoflurane. Weight of the mice varied from 19 to 30 g. Mice were killed at 31–36 weeks of age and the synaptic plasma membranes isolated.

Synaptic plasma membranes were prepared using a method of Jones and Matus (1974), and the activities of $Na^+ + K^+$-ATPase and acetylcholinesterase were measured in each of the brain subfractions (Koblin, Dong and Eger, 1979). Procedures for the analyses of synaptic membrane phospholipid, fatty acid, and cholesterol compositions have been presented elsewhere in detail (Koblin, Dong and Eger, 1979).

RESULTS

SS mice had higher anaesthetic requirements than the LS mice (table I). Nitrous oxide and enflurane requirements, as measured by the rolling-response test, were 34% and 20% greater in SS mice, respectively. Isoflurane requirement in SS mice, as measured by the tail-clamp procedure, was 39% greater. However, isoflurane requirement, as defined by the rolling-response test, was not significantly different between SS and LS mice (table I).

Synaptic plasma membrane fatty acid compositions were essentially identical in LS and SS mice (table II). For the phosphatidylcholine, phosphatidylserine and phosphatidylethanolamine fractions, fatty acid compositions for the LS and SS mice differed by no more than 1.0%. For the minor phospholipid components, sphingomyelin and phosphatidylinositol, the errors involved in the fatty acid analyses were larger because of the limited amount of material, and the mean fatty acid compositions occasionally differed by as much as 4.8% (table II). Only the arachidonate (20 : 4) content of the phosphatidylcholine fraction (table II) differed significantly ($P < 0.01$) between the two groups. Since 47 comparisons were made, the finding of one significant difference might be expected to occur by chance.

The synaptic membrane phospholipid compositions and the cholesterol/phospholipid molar

TABLE I. *Anaesthetic potencies of inhaled agents in long-sleep and short-sleep mice. * Anaesthetic potencies in long-sleep mice are significantly different from short-sleep mice* (P *<0.001*)

Anaesthetic	Method of testing	ED_{50} (atm) ± SEM	
		Long-sleep mice	Short-sleep mice
Nitrous oxide	Rolling-response	1.23 ±0.025*	1.65 ±0.032
Enflurane	Rolling-response	0.0124 ±0.00019*	0.0149 ±0.00031
Isoflurane	Rolling-response	0.00596 ±0.00014	0.00608 ±0.00018
Isoflurane	Tail-clamp	0.0118 ±0.00103*	0.0164 ±0.00076
n		17	19

TABLE II. *Phospholipid fatty acid compositions of synaptic membranes isolated from long-sleep (LS) and short-sleep (SS) mice (fatty acid compositions expressed as weight % of the listed fatty acids.) * Fatty acids are expressed in the form* x : y *(n-z), where* x *is the number of carbon atoms in the fatty acid chain,* y *is the number of double bonds and* z *is the number of carbon atoms from the terminal methyl group end of the fatty acid chain at which the first unsaturation occurs. Thus, linoleic acid, 18 : 2 (n-6), is 18 carbon atoms long and has two double bonds occurring between the 6th and 7th and between the 9th and 10th carbon atoms from the terminal methyl group. † Mean values ± SEM for six different synaptic membrane preparations for the short-sleep mice and five different synaptic membrane preparations for the long-sleep mice. ‡Arachidate (20 : 0) and linolenate (18 : 3 (n-6)) co-chromatographed, and the values listed represent the sum of the two components. § Significantly different from each other at* P *<0.01*

Fatty acid	Sphingomyelin		Phosphatidyl-choline		Phosphatidyl-serine		Phosphatidyl-inositol		Phosphatidyl-ethanolamine	
	LS	SS	LS	SS	LS	SS	LS	SS	LS	SS
16:0	12.6±0.2†	12.9±0.9	53.6±0.6	53.9±0.3	1.4±0.2	1.4±0.2	10.5±1.0	9.1±0.4	9.5±0.2	9.0±0.2
16:1	0.4±0.4	0.8±0.5	0.9±0.04	0.9±0.1	0.1±0.02	0.1±0.1			0.1±0.02	0.1±0.03
18:0	79.4±3.0	74.6±2.4	12.1±0.1	12.3±0.1	45.2±0.6	45.2±0.9	43.7±0.7	44.9±1.4	28.5±0.2	28.9±0.5
18:1 (n-9)	4.9±1.9	8.0±1.1	22.8±0.3	22.7±0.2	5.1±0.7	6.1±0.6	6.8±1.0	5.6±0.2	7.2±0.4	7.4±0.3
18:2 (n-6)			0.4±0.03	0.3±0.1						
18:3 (n-6) and/or 20:0†	2.6±0.7	3.6±0.8	0.1±0.03	0.1±0.1	0.2±0.1	0.2±0.1	0.4±0.2	0.1±0.1	0.1±0.03	
20:1			1.0±0.06	1.0±0.03	0.3±0.04	0.2±0.04			0.5±0.04	0.6±0.0
20.2			0.2±0.02	0.2±0.02						
20·3 (n-6)			0.2±0.02	0.2±0.02	0.2±0.04	0.3±0.1	0.2±0.12	0.1±0.1	0.2±0.03	0.2±0.02
20:4 (n-6)			4.4+0.1§	3.9±0.1	1.6±0.1	1.5±0.1	33.6±1.7	34.2±1.9	12.0±0.2	11.7±0.2
22:4 (n-6)			0.4±0.03	0.4±0.04	3.3±0.1	3.3±0.1			4.9±0.1	4.9±0.1
22:5 (n-6)				0.1±0.1	0.5±0.07	0.5±0.1			0.2±0.1	0.3±0.1
22:5 (n-3)					0.3±0.6	0.4±0.2			0.3±0.1	0.4±0.1
22 . 6 (n-3)			3.9±0.2	4.1±0.1	41.9±0.6	40.9±0.8	4.6±0.5	5.6±1.2	35.7±0.2	36.4±0.5

ratios were similar for the LS and SS mice (table III). Phospholipid compositions varied by no more than 0.9%. No significant differences in phospholipid or cholesterol content were found.

Acetylcholinesterase and $Na^+ + K^+$-ATPase activities were three- to four-fold greater in the synaptic-plasma-membrane-enriched fraction than in the whole brain homogenate. Synaptic membrane $Na^+ + K^+$-ATPase activities (at 37 °C) were 32.6 ± 2.7 for the LS mice and 35.5 ± 10.2 for the SS mice (mean ± SEM). Synaptic membrane acetylcholinesterase activities were 20.6 ± 5.2 and 26.0 ± 4.0 for the LS and SS mice, respectively. Enzyme activities are expressed as µmol of substrate consumed per milligram of protein per hour. The enzymatic activities measured in brain subfractions of the SS mice did not differ significantly from those of the LS mice.

TABLE III. *Phospholipid compositions and cholesterol/phospholipid molar ratios of synaptic plasma membranes isolated from long-sleep and short-sleep mice. *Calculated as % phosphate composition. †Values are mean ± SEM from six separate synaptic plasma membrane preparations from the short-sleep and five separate synaptic plasma membrane preparations from the long-sleep mice. ‡Calculated from the amount of cholesterol recovered and the amount of phosphate recovered in the phospholipid fractions from the TLC plate*

	Long-sleep	Short-sleep
Sphingomyelin*	4.3 ±0.5†	4.4 ±0.5
Phosphatidylcholine	39.3 ±0.5	39.3 ±1.3
Phosphatidylserine	15.7 ±0.6	15.8 ±0.8
Phosphatidylinositol	3.9 ±0.3	3.3 ±0.3
Phosphatidylethanolamine	36.8 ±0.9	37.7 ±1.0
Cholesterol/phospholipid molar ratio‡	0.585 ±0.0080	0.584 ±0.0180

DISCUSSION

The different ethanol-induced sleep-times in LS and SS mice are thought to result from differences in the central nervous system response to ethanol, since both lines of mice have identical rates of ethanol elimination and identical hepatic alcohol dehydrogenase and aldehyde dehydrogenase activities (Heston et al., 1974). The SS mice awaken at greater blood alcohol concentrations (Erwin et al., 1976). Similarly, our experiments were conducted after almost complete equilibration and hence exclude pharmacokinetics or metabolism as explanations for the difference in anaesthetic requirements seen between the LS and the SS mice. Thus, the difference probably results from different central nervous system sensitivities to anaesthetics.

Although our results support the hypothesis that the SS mice are more resistant to the effects of anaesthetics, there are quantitative differences that cannot be entirely explained. The greatest difference (between the anaesthetic requirement for SS and LS mice) was seen with isoflurane using the tail-clamp test. The smallest difference (2%) was seen with isoflurane using the righting reflex. In part, this may have resulted from the different sensitivities or reflex arcs assessed by the two tests. However, the negative results for the righting reflex with isoflurane contrast with the significant results seen with nitrous oxide and enflurane (an isomer of isoflurane). We cannot explain these differences.

The response of LS and SS mice to other depressant agents also varies. ED_{50} for loss of righting reflex following administration of methanol, butanol or *t*-butanol is approximately two-fold greater for SS than LS mice (Erwin et al., 1976). However, the diethyl ether (Erwin et al., 1976) or halothane (Baker, Melchior and Deitrich 1980) ED_{50} for loss of righting reflex are not significantly different. Sleep-times following chloral hydrate or trichloroethanol do not differ (Erwin et al., 1976). Pentobarbitone sleep-times are significantly longer in SS mice, but the pentobarbitone concentrations in the brain are the same in both strains at the time of awakening, suggesting equal sensitivities of the central nervous system to pentobarbitone (Siemens and Chan, 1976). It appears that the differential effect of ethanol in these two strains is greater than that of inhaled anaesthetics, since the blood ethanol concentrations upon awakening in SS mice are 65% greater than in LS mice (Erwin et al., 1976), whereas the largest difference in inhaled anaesthetic requirement was 39% (table I). These variable results suggest that the genetic selection which produced the LS and SS mice did not result in a constant central nervous system sensitivity or resistance to depressants.

Despite this variability, previous experiments and our study suggest that differences exist in the brain sensitivities of LS and SS mice to both inhaled anaesthetics and alcohol. These differences might arise from structural alterations in the brain, particularly those in neuronal membrane lipid composition. The excellent correlation between lipid solubility and anaesthetic potency implies a hydrophobic site of action (Eger et al., 1969; Miller et al., 1972), and is expressed by the low variability of the product of the anaesthetic ED_{50} for an agent and its oil–gas partition coefficient. For the rolling-response ED_{50} in mice, this product is restricted to values between 0.55 (for isoflurane) and 2.83 for agents which vary by more than a 10 000-fold range of anaesthetic partial pressures (Kent et al., 1977; Smith et al., 1977). Also, both general anaesthetics (Vanderkooi et al., 1977: MacDonald, 1978; Pang, Chang and Miller, 1979; Rosenberg, 1979) and alcohol (Chin and Goldstein, 1977; Hill, 1978; Johnson et al., 1979; Mastrangelo et al., 1979) can perturb the lipid bilayer structure of phospholipid model membranes and biological membranes. A perturbation of membrane lipids may influence the functional properties of membrane proteins (Korenbrot, 1977), and an anaesthetic-induced (or alcohol-induced) alteration in the physical state of nerve membrane lipids may interfere with transmitter release or ionic conductance mechanisms (Trudell, 1977). That is, the SS mice might possess a neuronal membrane lipid composition which could resist the perturbing properties of inhaled anaesthetics and alcohol. However, the synaptic membrane fatty acid, phospholipid and cholesterol compositions were essentially identical in the SS and LS mice (tables II and III). The only significant difference found was a lower arachidonate (20 : 4) content in the phosphatidylcholine fraction of the SS animals (3.9%) compared with the LS mice (4.4%). Finding a significant difference between one pair of values of the 47 pairs presented in table II is not surprising, and a decrease in arachidonate content was not seen in any of the other phospholipid fractions. It therefore appears that the different susceptibilities of SS and LS mice to anaesthetics and alcohol cannot be caused by an altered synaptic plasma membrane lipid composition. It is possible, however, that our measurements are not sensitive enough to detect important differences in synaptic membrane lipid composition between the LS or SS mice. In addition, if the differences in anaesthetic requirement and alcohol response are the result of a change in a small brain region, or result from an alteration in neuronal membranes other than synaptic membranes, the present techniques would not detect such a change.

These experiments did not reveal the central nervous system differences that cause the different sensitivities of LS and SS mice to inhaled agents and alcohol. Possibly the two strains differ in their neurotransmitter content or in their affinity to, or numbers of, neurotransmitter receptors. Indeed, rats genetically selected for a high alcohol preference have a higher serotonin (Ahtee and Eriksson, 1973) and a higher dopamine (Ahtee and Eriksson, 1975) content than rats selected for low alcohol preference. Also, an alteration in monoamine concentrations can influence anaesthetic requirement (Johnston, Way and Miller, 1974; Roizen et al., 1978). Whether differences in the neurotransmitter systems of LS and SS mice can explain their altered sensitivities to inhaled anaesthetics and alcohol remains to be determined.

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EXIGENCES ANESTHESIQUES DETERMINEES SUR DES SOURIS ELEVEES SELECTIVEMENT DE MANIERE A AVOIR DES DIFFERENCES DE SENSIBILITE A L'ETHANOL

RESUME

Les exigences anesthésiques requises pour le protoxyde d'azote, l'enflurane et l'isoflurane ont été déterminées sur des souris élevées sélectivement afin d'avoir une sensibilité (souris à "sommeil long") ou une résistance (souris à "sommeil court") à l'alcool. Les exigences du protoxyde d'azote et de l'enflurane, mesurées par l'essai de réaction au tournis de la souris, ont été respectivement de 34% et de 20% plus grandes chez les souris à sommeil court que chez les souris à sommeil long. Bien que les exigences de l'isoflurane aient été de 39% plus grandes, lorsqu'elles ont été mesurées par l'essai de pincement de la queue, elles n'ont pas été sensiblement différentes de celles obtenues lors de la mesure par l'essai de réaction au tournis de la souris. L'exigence anesthésique la plus importante pour la souris à sommeil court n'a pas été associée à un phospholipide différent de la membrane synaptique, à un acide gras ou à une composition de cholestérol.

ANÄSTHESIEERFORDERNIS BEI SELEKTIV NACH UNTERSCHIEDEN IN ÄTHANOL-EMPFINDLICHKEIT GEZÜCHTETEN MÄUSEN

ZUSAMMENFASSUNG

Die Anasthesieerfordernisse für Stickoxyd, Enfluran und Isofluran wurden bei Mausen bestimmt, die selektiv auf ihre Anfälligkeit ("Langsschlafermäuse") oder ihre Resistenz ("Kurzschläfermäuse") auf, bezw. gegen Alkohol gezuchtet worden waren. Der Bedarf an Stickoxyd und Enfluran, durch den Rollreaktionstest gemessen, war jeweils um 34% und um 20% grosser bei Kurz- als bei Langschlafermausen.Obwohl der Isofluran-Bedarf bei Messung durch den Schwanzklemmentest um 39% grösser war, war er im Rollreaktionstest nicht wesentlich anders. Der höhere Anasthesiebedarf bei Kurzschläfermausen hing nicht mit einem verschiedenen synaptischen Membran-Phospholipoid, mit Fettsaure oder mit Cholesterolzusammensetzung zusammen.

REQUISITOS ANESTESICOS EN EL RATON SELECTIVAMENTE CRIADO, EN LO TOCANTE A LAS DIFERENTES SENSIBILIDADES AL ETANOL

SUMARIO

Las necesidades anestésicas relativas al óxido nitroso, al enflurano y al isoflurano se determinaron en ratones selectivamente criados para el estudio de su susceptibilidad (ratón de "sueño prolongado") o resistencia (ratón de "sueño corto") al alcohol. Los requisitos de óxido nitroso y de enflurano, medidos mediante la prueba de respuesta móvil, fueron superiores en un 34% y un 20%, respectivamente, para el ratón de sueño corto en comparación con el de sueño prolongado. Aunque el requisito de isoflurano fue un 39% superior cuando se midió mediante la prueba de grapa de rabo, dicho requisito no fue significativamente diferente cuando se midió mediante la prueba de respuesta móvil El mayor requisito anestésico para el ratón de sueño corto no vino asociado con una diferente composición de colesterol, de ácido adiposo ni de la fosfolipina de la membrana sináptica.

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DEPRESSION OF HYPOXIC PULMONARY VASOCONSTRICTION BY SODIUM NITROPRUSSIDE AND NITROGLYCERINE

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SUMMARY

The pulmonary vasoconstrictor response to the unilateral administration of 7% oxygen was studied in 10 anaesthetized dogs in which the lungs were mechanically ventilated. The distribution of blood flow between the two lungs was measured continuously by recording the radioactivity in the mixed expired gas from each lung during the infusion i.v. of xenon-133. Infusions of nitroglycerine and sodium nitroprusside which produced the same decrease in mean aortic pressure produced similar decreases in hypoxic pulmonary vasoconstriction. The reduction in arterial Po_2 during unilateral hypoxia was greater when the hypoxic vasoconstrictor response was depressed by drugs than it was during the control periods, although mixed venous Po_2 was unchanged. It is concluded that both drugs may cause hypoxaemia by increasing the blood flow to alveoli with a low ventilation/perfusion ratio.

Sodium nitroprusside (SNP) and nitroglycerine (NG) are used to treat arterial hypertension in patients undergoing coronary artery bypass surgery. However, both drugs reduce arterial oxygen tension (Wildsmith, Drummond and MacRae, 1975; Seltzer, Doto and Jacoby, 1976; Kopman et al., 1978). There appear to be three possible mechanisms which could decrease Pa_{O_2}. First, the drug might produce a reduction in venous return caused by dilatation of capacitance vessels and so decrease cardiac output and mixed venous Po_2 ($P\bar{v}_{O_2}$). In the presence of areas of lung with a low ventilation/perfusion ratio, the reduction in $P\bar{v}_{O_2}$ would cause a reduction in Pa_{O_2} even though the proportion of blood flowing through such areas was unchanged (Sykes, Young and Robinson, 1965). A second explanation is that the drug might cause pulmonary vasodilatation and decrease pulmonary artery pressure. If there were underventilated alveoli in the dependent zones of the lung, the reduction in pulmonary artery pressure might decrease the flow to the normally ventilated portions of the lung and so increase the proportion of blood flowing through the underventilated alveoli even though the absolute flow through such alveoli was unchanged (Colley and Cheney, 1977; Colley, Cheney and Butler, 1977). The third possibility is that the proportion of blood flowing through underventilated lung zones might be increased by a drug-induced depression of the hypoxic vasoconstrictor mechanism which normally diverts flow away from areas of lung with a low alveolar Po_2 (Hughes, 1975).

Studies in dogs indicate that SNP may depress this mechanism (Colley, Cheney and Hlastalä, 1979; Hill, Sykes and Reyes, 1979). The present experiments were designed to compare the effects of NG and SNP on the pulmonary vasoconstrictor response to unilateral alveolar hypoxia.

METHODS

The experiments were performed on 10 dogs of varied breed (weight 16–24 kg). They were anaesthetized with thiopentone 20–30 mg kg^{-1} i.v. supplemented by increments of pentobarbitone to a total of 20 mg kg^{-1}. The animals were placed supine in a V-shaped trough and the lungs ventilated mechanically. Pancuronium 2–4 mg was injected at intervals to ensure no spontaneous respiratory activity. These three drugs have been shown to have no effect on the hypoxic vasoconstrictor response. Cannulae were inserted to the femoral vessels for pressure recording, blood sampling, dye injection and withdrawal, and infusion of xenon-133. Two catheters, one of the Swan–Ganz type, were passed into the pulmonary artery for blood sampling and simultaneous recording of pulmonary artery (P_{PA})

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and pulmonary wedge pressures (P_{PAW}) and a separate i.v. infusion line was established for fluid and drug administration. Tracheotomy was performed and a double-lumen tracheal divider passed (Seed and Sykes, 1972). After inflation of the cuff, accurate placement of the tube was checked by measurements of the tidal volume issuing from each lung. The absence of leaks was demonstrated by pressurizing each lung to +3.0 kPa whilst the opposite limb of the tube was connected to a tube placed under water. Each limb of the tube was then connected to a separate non-rebreathing valve and second-stage ventilator circuit which could be driven by the main ventilator at 15 b.p.m. (Reyes et al., 1979). The tidal volume to each lung was adjusted to produce equal end-tidal carbon dioxide concentrations of 4–4.5% and then kept constant during the experiment.

The distribution of pulmonary blood flow between the two lungs was measured continuously by infusing xenon-133 dissolved in 50–100 ml of normal saline at a rate of 1–2 mCi h^{-1} using a Braun continuous infusion pump. Approximately 95% of the xenon was evolved to the alveoli during its passage through the lungs and then washed out by the tidal ventilation.

The expired gas from each lung was passed through a fan-assisted mixing unit and the mixed expired gas then circulated through a glass coil situated within the collimator of a scintillation detector. The output from each detector was processed to yield a continuous record of the radioactivity issuing from each lung. Since tidal volumes were initially matched to the blood flow to each lung, the initial ratio of right/left (R/L) radioactivity was 1. When hypoxic vasoconstriction was induced in the left lung by ventilating it with hypoxic gas mixture, the radioactivity on that side decreased and the radioactivity on the opposite side increased. This caused an increased R/L ratio of radioactivity which reflected the magnitude of diversion of blood flow away from the hypoxic lung (Sykes, Hill et al., 1977). In this study, the percentage diversion was calculated from the equation:

$$\%\ \text{diversion} = \frac{C_R - C_L}{C_I} \times 100$$

where C_I = mean counts from both lungs during bilateral ventilation with oxygen; C_R, C_L = counts from right and left lungs during unilateral hypoxia.

Vascular and airway pressures were monitored continuously with Consolidated Dynamics strain gauges and a Devices M 19 heated stylus recorder. Oesophageal temperature was monitored with a thermistor probe and body temperature maintained at 37 ± 1 °C.

Cardiac output was determined in triplicate with indocyanine green dye using a calibrated Gilford system, the curves being analysed by the method of Simons and White (1976). Blood-gas tensions and pH measurements were made on two separate electrode systems (Radiometer ABL1 and the standard Radiometer system) which were calibrated with previously analysed gases and repeatedly checked with tonometered blood samples (Sykes et al., 1970; Selman and Tait, 1976).

The right lung was ventilated throughout with pure oxygen. The left lung was initially ventilated with oxygen and the hypoxic vasoconstrictor response elicited by switching the ventilating gas mixture to 7% oxygen in nitrogen. This gas mixture yields alveolar oxygen tensions in the mixed venous range.

The initial measurements of xenon count, cardiac output, vascular and airway pressures, end-tidal carbon dioxide concentration and blood-gases were made 20–30 min after stable conditions had been achieved with both lungs ventilated with oxygen. The ventilating gas to the left lung was then changed to 7% oxygen and a second set of measurements made 10–15 min later when vascular pressures and xenon counts were stable. Both lungs were again ventilated with oxygen and an infusion of the drug started. The dose rate was adjusted to produce a mean arterial pressure of 105–110 mm Hg, the lowest that could usually be achieved with NG, and a third set of measurements was made 10 min later. The drug infusion was continued and the left lung switched to 7% oxygen, the fourth set of measurements being made when conditions had stabilized after a further 10–15 min. The drug was then discontinued and both lungs ventilated with oxygen until the pressures had returned to pre-existing values. A fifth set of measurements on bilateral oxygen was made 30–40 min after discontinuing the drug and a sixth set 10–15 min after again ventilating the left lung with 7% oxygen. The fifth and sixth sets of measurements also served as control measurements for the second drug which was administered in a manner similar to the first. Hypoxic responses were obtained during the period of administration of the second drug and 30–40 min after withdrawing the drug. The order in which the SNP and NG were administered was varied in a random manner so that five animals received SNP as the first drug and five animals NG first. The results were subjected to an analysis of variance followed by *t* tests where indicated. The statistical analysis compared the effects of each drug with the controls before and after administration of the drug and also tested for the effect of time and sequence of drug administration. The drugs used in these studies were SNP (Roche) 0.01% (mean dose 9.1 mg, range 6.7–50 mg) and NG (Arnar-Stone Laboratories Inc.) 0.1% (mean dose 17.5 mg, range 10–40 mg).

RESULTS

Control periods

The three sets of control values (C_1, C_2, and C_3) on bilateral oxygen and unilateral hypoxia were grouped according to the sequence in which they were obtained. During bilateral ventilation with oxygen the only measurement which changed significantly during the experiment was $P_{\overline{PAW}}$. This increased from 2.6 mm Hg at C_1 to 4.6 mm Hg at C_3.

Unilateral ventilation with 7% oxygen resulted in significant reductions in Pa_{O_2}, $P\bar{v}_{O_2}$ and left lung end-tidal carbon dioxide concentration (FE'_{CO_2}) and a significant increase in FE'_{CO_2} in the right (oxygenated) lung (table I). However, it produced no significant change in cardiac output, vascular and airway pressures, Pa_{CO_2}, base excess or haemoglobin concentration. Unilateral hypoxia reduced the proportion of blood flowing to the hypoxic lung, the magnitude of this response increasing with time.

Effect of drugs

The variables measured during the period of drug administration were compared with the means of the control values obtained before and after the infusion (table II).

During bilateral oxygen ventilation, NG produced significant reductions in cardiac output ($\dot{Q}$), mean aortic pressure ($P_{\overline{AO}}$), $P_{\overline{PA}}$ and $P_{\overline{PAW}}$. During the same conditions, SNP produced significant decreases in $P_{\overline{AO}}$, $P_{\overline{PA}}$ and $P_{\overline{PAW}}$ and a significant increase in heart rate (HR). There were no significant changes in any of the other measured variables.

$P_{\overline{AO}}$, $P_{\overline{PAW}}$ and Pa_{O_2} were significantly reduced during unilateral hypoxia and NG administration compared with the means of the before and after control values during unilateral hypoxia. SNP produced significant reductions in $P_{\overline{AO}}$, $P_{\overline{PA}}$ and Pa_{O_2} and a significant increase in HR compared with the means of unilateral hypoxia control measurements. During unilateral hypoxia, both drugs produced a similar degree of depression of

TABLE I. *Significant changes in measurements recorded during control periods. Results grouped according to the time sequence in which they were obtained* (C_1, C_2 *and* C_3)*. The left lung was subjected to hypoxia. The end-tidal carbon dioxide* (FE'_{CO_2}) *comparisons were based on the average results from the three control periods*

		C_1		C_2		C_3		
		O_2/O_2	$O_2/7\%O_2$	O_2/O_2	$O_2/7\%O_2$	O_2/O_2	$O_2/7\%O_2$	C_3 v C_1
% Reduction in left lung blood flow	mean		31.5		37.8		48.5	$P<0.05$
	SD		±20.2		±8.7		±16.4	
								$O_2/7\%O_2$ v O_2/O_2
Pa_{O_2} (kPa)	mean	56.9	17.2	51.9	18.2	54.2	20.5	$P<0.001$
		±8.6	±3.9	±15.7	±6.9	±14.3	±7.7	
$P\bar{v}_{O_2}$ (kPa)	mean	7.4	6.1	6.8	5.9	6.9	6.0	$P<0.001$
	SD	±0.9	±0.9	±1.0	±1.0	±1.2	±1.3	
FE'_{CO_2} (left) (%)	mean	4.4	4.1	4.4	3.9	4.5	3.8	$P<0.001$
	SD	±0.4	±0.4	±0.5	±0.4	±0.5	±0.6	
FE'_{CO_2} (right) (%)	mean	4.5	4.8	4.5	4.8	4.6	4.9	$P<0.01$
	SD	±0.4	±0.5	±0.6	±0.6	±0.5	±0.5	

TABLE II *Cardiorespiratory measurements (mean ± SD) at each stage of the experiment*

	Before drug		NG		After drug			
	A	B	C	D	E	F	C *v.* mean of A and E	D *v.* mean of B and F
Variables	O_2/O_2	$O_2/7\%O_2$	O_2/O_2	$O_2/7\%O_2$	O_2/O_2	$O_2/7\%O_2$		
$\dot{Q}$ (litre min^{-1})	2.01 ±0.69	1.90 ±0.66	1.60 ±0.44	1.85 ±0.65	1.87 ±0.52	1.85 ±0.58	$P<0.01$	n.s.
$P_{\overline{AO}}$ (mm Hg)	143.0 ±27.3	143.0 ±18.4	109.2 ±17.4	115.7 ±19.5	134.7 ±13.1	137.1 ±14.4	$P<0.0001$	$P<0.0001$
$P_{\overline{PA}}$ (mm Hg)	10.50 ±1.58	12.25 ±2.07	9.85 ±1.60	12.40 ±2.71	12.95 ±2.83	14.7 ±2.87	$P<0.02$	n.s.
$P_{\overline{PAW}}$ (mm Hg)	3.03 ±1.47	4.05 ±2.28	2.40 ±1.56	2.45 ±3.18	4.90 ±2.55	5.60 ±2.71	$P<0.01$	$P<0.01$
HR (beat min^{-1})	164.3 ±39.1	165.7 ±31.7	187.9 ±35.2	185.1 ±27.4	179.3 ±22.7	182.6 ±21.8	n.s	n.s.
Pa_{O_2} (kPa)	57.21 ±8.04	18.96 ±3.39	55.33 ±11.39	14.09 ±3.04	51.91 ±15.52	18.69 ±7.20	n.s.	$P<0.03$
$P\bar{v}_{O_2}$ (kPa)	7.22 ±1.11	5.98 ±0.89	6.65 ±1.01	5.62 ±0.74	6.85 ±1.06	6.02 ±0.82	n.s.	n.s.
Pa_{CO_2} (kPa)	4.79 ±0.49	4.81 ±0.90	4.70 ±0.50	4.79 ±0.63	4.89 ±0.57	4.85 ±0.62	n.s.	n.s.

	Before drug		SNP		After drug			
	G	H	I	J	K	L	I *v.* mean of G and K	J *v.* mean of H and L
Variables	O_2/O_2	$O_2/7\%O_2$	O_2/O_2	$O_2/7\%O_2$	O_2/O_2	$O_2/7\%O_2$		
$\dot{Q}$ (litre min^{-1})	2.12 ±0.69	1.94 ±0.62	1.83 ±0.61	2.16 ±0.83	1.99 ±0.61	1.95 ±0.56	n.s.	n.s.
$P_{\overline{AO}}$ (mm Hg)	133.5 ±15.5	138.2 ±15.5	103.2 ±14.8	107.4 ±14.3	143.0 ±24.3	139.5 ±17.7	$P<0.0001$	$P<0.0001$
$P_{\overline{PA}}$ (mm Hg)	12.0 ±2.58	13.40 ±1.95	10.10 ±2.99	11.27 ±2.83	12.70 ±3.36	14.95 ±3.78	$P<0.01$	$P<0.01$
$P_{\overline{PAW}}$ (mm Hg)	3.75 ±2.93	4.51 ±3.07	2.40 ±2.39	2.65 ±2.91	3.90 ±2.01	4.0 ±2.39	$P<0.05$	n.s.
HR (beat min^{-1})	180.6 ±22.1	185.6 ±26.0	195.9 ±34.6	194.7 ±34.1	159.2 ±37.9	164.4 ±31.5	$P<0.01$	$P<0.05$
Pa_{O_2} (kPa)	51.57 ±15.87	16.41 ±6.96	54.09 ±13.53	12.07 ±2.84	54.13 ±14.44	20.05 ±7.60	n.s.	$P<0.01$
$P\bar{v}_{O_2}$ (kPa)	7.0 ±0.83	5.93 ±0.61	6.89 ±1.13	5.68 ±1.04	6.84 ±1.19	5.88 ±1.16	n.s.	n.s.
Pa_{CO_2} (kPa)	4.89 ±0.56	4.82 ±0.61	4.78 ±0.68	5.04 ±0.56	4.98 ±0.65	5.18 ±0.93	n.s.	n.s.

the pulmonary vasoconstrictor response to alveolar hypoxia (table III). However, Pa_{O_2} during unilateral hypoxia was significantly less during SNP administration than during infusion of NG. This was probably because of the slightly greater inhibition of the hypoxic vasoconstrictor response by SNP.

DISCUSSION

The study demonstrates that when NG and SNP were infused at dose rates which produced equal reductions in mean aortic pressure they produced similar degrees of depression of the pulmonary vasoconstrictor response to alveolar hypoxia. However, the slightly increased inhibition of the

TABLE III. *Percentage decrease in blood flow in left lung in response to unilateral hypoxia*

Dog no.	A Before NG	B During NG	C After NG	D Before SNP	E During SNP	F After SNP
1	40.0	32.6	30.0	30.0	10.0	27.2
2	27.0	34.0	40.0	40.0	16.9	57.6
3	30.8	29.5	39.0	18.6	0.0	30.8
4	20.7	10.8	40.0	40.0	22.2	37.7
5	26.6	0.0	24.4	24.4	23.0	48.2
6	32.9	13.8	34.3	23.3	11.1	32.9
7	35.0	35.0	35.5	20.0	13.6	35.0
8	44.2	17.2	66.6	70.3	36.5	44.2
9	31.3	19.0	50.0	50.0	46.3	62.5
10	50.6	36.0	76.6	57.1	32.3	50.6
Mean	33.9	22.8	43.6	35.4	19.2	42.7
SD	±8.9	±12.4	±16.4	±20.6	±15.1	±11.9
Significance		$P<0.01$	$P<0.01$		$P<0.01$	$P<0.01$

response by SNP produced a significantly greater reduction in arterial Po_2 during unilateral hypoxia, although the mean values of mixed venous Po_2 were the same. These results were confirmed by the changes in end-tidal carbon dioxide which normally reflect changes in blood flow.

The unilateral ventilation hypoxia model used in this study may be criticized because it does not exactly simulate the underventilated or atelectatic areas of the lung.

The first criticism is that the alveolar Po_2 (PA_{O_2}) values during ventilation hypoxia might not be comparable to those in an underventilated area of lung. End-tidal gas samples and sampling of blood from the pulmonary veins draining a lung or lobe ventilated with 7–9% oxygen have confirmed that this gas mixture produces PA_{O_2} values in the range 5–6 kPa when pulmonary vasoconstriction is established and alveolar Pco_2 (PA_{CO_2}) is reduced.

The second criticism is that the maintenance of constant ventilation when blood flow is reduced by alveolar hypoxia results in a reduction in PA_{CO_2}, whereas PA_{CO_2} is normally increased in an underventilated area of lung. Since a reduction in PA_{CO_2} decreases the magnitude of the response to hypoxia, the greater reduction in PA_{CO_2} during the control periods would have tended to minimize the differences between the control hypoxic responses and those recorded during the period of drug administration. It is therefore likely that the decrease in pulmonary vasoconstriction recorded in the present experiments underestimated the effect of the drug. Other experiments have demonstrated that the maintenance of constant end-tidal Fco_2 values does not alter the qualitative results (Sykes et al., 1975; Hurtig, Tait and Sykes, 1977).

The third criticism is that regional lung volume and tidal volume are maintained at normal values. It is not known how hypoxic vasoconstriction varies with lung volume, but it is now believed that most of the reduction in blood flow in atelectatic lungs is a result of hypoxic pulmonary vasoconstriction. This can be reversed by drug administration (Barer, 1966; Benumof, 1979). It seems unlikely, therefore, that the use of ventilation hypoxia will affect the qualitative effect produced by the drugs.

The model has a number of advantages. First, factors which may affect the pulmonary circulation, such as changes in pulmonary vascular pressures, acid–base balance and temperature, are applied equally to both lungs. Airway pressures are closely controlled and both cardiovascular and respiratory variables can be monitored during the experiment. Second, the radio-isotope method of measuring flow is accurate, utilizes relatively little radioactivity and provides a continuous measurement of blood flow (Sykes, Hill et al., 1977). This enables the response to be monitored visually so that other measurements can be correctly synchronized with the peak response. It is believed that the advantages outweigh the disadvantages and that this model provides a satisfactory method of studying the problem.

The decreased vasoconstriction in the hypoxic lung observed during the period of drug administration could have been produced by a generalized reduction in pulmonary vascular tone or by an inhibition of the pulmonary vasoconstrictor response to alveolar hypoxia. In the present experiments both drugs produced a small increase in pulmonary vascular resistance. However, both P_{PA} and P_{PAW} decreased, so that the apparent increase in resistance could have been caused by a reduction in the cross-sectional area of the perfused vascular bed. Mentzer and Nolan (1977a) demonstrated that NG caused vasodilatation in a left lower lobe perfusion preparation in new-born puppies and Kaplan, Dunbar and Jones (1976) found that infusion at a mean dose rate of 0.96 $\mu g\ kg^{-1}\ min^{-1}$ reduced pulmonary vascular resistance in patients undergoing open-heart surgery. Since alveolar oxygen tensions were normal or increased during these studies, it seems reasonable to conclude that the drug can act as a pulmonary vasodilator. There is also evidence that SNP may produce pulmonary vasodilatation. For example, Stinson and others (1975) found that SNP reduced pulmonary vascular resistance in patients after open-heart surgery. However, Mentzer and Nolan (1977b), Colley, Cheney and Hlastalä (1979), and Hill, Sykes and Reyes (1979) found no evidence of decreased pulmonary vascular resistance in dogs.

If a drug produces vasodilatation by reducing wall tension in the pulmonary arterioles, the effect will depend on the radius of the vessel. According to the Laplace relationship, $P = 2\tau/R$, a given reduction in wall tension should produce a proportionally larger increase in radius when the vessel is constricted than when it is dilated. The administration of a vasodilator drug might therefore result in redistribution of flow towards the previously vasoconstricted vascular bed.

There is, however, increasing evidence which indicates that many drugs have a direct action on the hypoxic vasoconstrictor mechanism. For example, in isolated lungs perfused at constant flow, drugs such as ether and trichloroethylene inhibit the pressor response to alveolar hypoxia without altering pulmonary vascular tone (Sykes et al., 1973; Hurtig, Tait and Sykes, 1977). Similar results have been obtained in the intact animal (Sykes et al., 1975; Sykes, Hurtig et al., 1977). Inhibition can also be produced by calcium antagonists (McMurtry et al., 1976) and by carbon monoxide (Miller and Hales, 1978). Furthermore, both pulmonary vaso-constrictor and -dilator drugs inhibit hypoxic pulmonary vasoconstriction. For example, dopamine is a pulmonary vasoconstrictor and isoprenaline is a vasodilator, yet dose rates which are equipotent in terms of their inotropic effect produce similar degrees of inhibition of the pulmonary vasoconstrictor response to hypoxia (Marin et al., 1979).

Areas with a low $P\text{A}_{O_2}$ are unlikely to exist in normal lungs, so it is not surprising that many of the drugs which are known to inhibit the pulmonary vasoconstrictor response do not produce hypoxaemia in animals or patients when the lungs are normal (Stone, Khambatta and Matteo, 1976; Colley, Cheney and Hlastalä, 1979). The unchanged Pa_{O_2} values on bilateral oxygen found in this study provide further confirmation that there is no increase in intrapulmonary shunt in normal lungs. However, depression of the pulmonary vasoconstrictor mechanism is probably an important cause of hypoxaemia in patients with severe ventilation/perfusion ratio abnormalities, particularly if collapse is present (Barer, 1966; Benumof, 1979). The effect will be accentuated if $P\bar{v}_{O_2}$ is simultaneously reduced by an imbalance between cardiac output and tissue oxygen consumpiton.

Hypoxic pulmonary vasoconstriction is depressed by a number of other factors, some of which may be particularly relevant to the patient with cardiac disease. For example, Benumof and Wahrenbrock (1975) and Scanlon and others (1978) have claimed that the response is diminished by high vascular pressures, whilst Hauge (1969) and Benumof and Wahrenbrock (1977) found that it was inhibited by hypothermia. Both these conditions may be found in patients undergoing cardiac surgery.

It is concluded that since NG and SNP appear to produce arterial hypoxaemia by depressing the hypoxic pulmonary vasoconstrictor response, their administration should be accompanied by oxygen enrichment of the inspired gases and careful monitoring of Pa_{O_2}.

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DEPRESSION DE LA VASOCONSTRICTION PULMONAIRE HYPOXIQUE PAR LE NITROPRUSSIATE DE SOUDE ET LA NITROGLYCERINE

RESUME

La réaction vasoconstrictrice pulmonaire à l'administration unilatérale de 7% d'oxygène a été étudiée sur 10 chiens anesthésiés, dont les poumons étaient ventilés mécaniquement La répartition du débit sanguin entre les deux poumons a été mesurée continuellement par enregistrement de la radioactivité des mélanges de gaz expirés de chaque poumon pendant la perfusion intraveineuse de xénon-133. Les perfusions de nitroglycérine et de nitroprussiate de soude qui produisent la même diminution de la pression aortique moyenne ont provoqué des diminutions similaires dans la vasoconstriction pulmonaire hypoxique. La réduction de la Po_2 artérielle pendant l'hypoxie unilatérale a été plus forte lorsque la réaction vasoconstrictrice hypoxique a été déprimée par des médicaments, qu'elle ne l'avait été pendant les périodes de contrôle,

bien que la Po_2 veineuse mélangée soit demeurée sans changement. On en a conclu que les deux médicaments peuvent provoquer l'hypoxémie en augmentant le débit sanguin allant aux alvéoles avec un faible rapport ventilation/perfusion.

DÄMPFUNG DER HYPOXISCHEN PULMONARGEFÄSSVERENGUNG DURCH NATRIUMNITROPRUSSID UND NITROGLYZERIN

ZUSAMMENFASSUNG

Die pulmonare Vasokonstriktorreaktion auf die einseitige Verabreichung von 7% Sauerstoff wurde bei 10 anästhesierten Hunden untersucht, deren Lungen mechanisch belüftet wurden. Die Blutflussverteilung zwischen den beiden Lungenflügeln wurde kontinuierlich gemessen, indem die Radioaktivitat des ausgeatmeten Gasgemisches aus jeder Lunge während einer Infusion von Xenon-133 (intravenös) aufgezeichnet wurde. Infusionen von Nitroglyzerin und Natriumnitroprussid, die den gleichen Abfall des mittleren Aortendrucks hervorriefen, bewirkten auch eine ahnliche Verringerung der pulmonaren hypoxischen Gefässverengung. Die Reduzierung von arteriellem Po_2 wahrend unilateraler Hypoxie war grösser, wenn die hypoxische Vasokonstriktorreaktion durch Drogen gedämpft wurde, als sie während der Kontrollperioden war, obwohl das gemischte venose Po_2 unverändert blieb. Daraus schliesst man, dass beide Drogen Hypoxämie verursachen können, indem sie die Blutzufuhr zu den Alveolen mit niedrigem Beluftungs/Durchstromungs-Verhaltnis erhöhen.

DEPRESION DE LA VASOCONSTRICCION HIPOXICA PULMONAR MEDIANTE NITROGLICERINA Y NITROPRUSIATO DE SODIO

SUMARIO

La respuesta vasoconstrictora pulmonar a la administración unilateral de 7% de óxigeno se estudió en 10 perros anestesiados en los que los pulmones se ventilaron por medios mecánicos. La distribución del flujo sanguíneo entre los dos pulmones se midió continuamente mediante el registro de la radioactividad existente en el gas mezclado de espiración procedente de cada uno de los pulmones, durante la infusión intravenoso de xenon-133. Las infusiones de nitroglicerina y de nitroprusiato de sodio que produjeron la misma disminución en la presión aórtica media produjeron, así mismo, disminuciones similares en la vasoconstricción hipóxica pulmonar. La reducción del Po_2 arterial durante la hipóxia unilateral fue mayor cuando la respuesta hipóxica vasoconstrictora se redujo mediante drogas de lo que fue durante los periodos de control, aunque el Po_2 mezclado de carácter venoso permaneció inalterado. La conclusión es, por lo tanto, que ambas drogas pueden ocasionar hipoxemia al incrementar el flujo sanguíneo al alveolo con una baja relación de ventilación/perfusión.

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INTERACTIONS OF ADRENERGIC BETA-RECEPTOR BLOCKADE (OXPRENOLOL) AND $P\text{CO}_2$ IN THE ANAESTHETIZED DOG: INFLUENCE OF INTRINSIC BETA-SYMPATHOMIMETIC ACTIVITY

P. FOËX AND W. A. RYDER

SUMMARY

Effects of change in Pa_{CO_2} on systemic and coronary haemodynamics and on coronary sinus blood-gases have been studied in 10 open-chested dogs in which the lungs were ventilated with 0.8% halothane in oxygen, before and after administration of oxprenolol 0.3 mg kg^{-1} i v. The hyperdynamic response of the circulation to hypercapnia was only marginally reduced after oxprenolol (cardiac output increased by 10% as opposed to 16% before oxprenolol) Before and after oxprenolol, hypocapnia caused large reductions of coronary blood flow (−24% and −20% respectively), while hypercapnia caused large increases of coronary blood flow (+59% and +34% respectively). Oxprenolol does not appear to modify significantly the circulatory response to arterial carbon dioxide tension.

Blockade of the adrenergic beta-receptors modifies responses of the circulation to changes in Pa_{CO_2} (Ledingham et al., 1970; Foëx and Prys-Roberts, 1974; Van den Bos, Drake and Noble, 1979). In the case of hypocarbia, the effect of adrenergic beta-blockade may be minimal. However, in the case of hypercarbia, blockade of the beta-receptors may result in withdrawal of an important inotropic support. The direct negative inotropic effect of carbon dioxide on the myocardium (Jerusalem and Starling, 1910; Pannier and Brutsaert, 1968; Foëx and Fordham, 1972) is thus unmasked and cardiovascular depression may occur. Intrinsic beta-sympathomimetic activity is a feature of the effect of some adrenergic beta-receptor antagonists. The enhancement of myocardial performance from intrinsic sympathomimetic activity (ISA) has been well documented in the isolated heart (Fitzgerald, Wale and Austin, 1972; Nayler and Chang, 1973) and it has also been observed in anaesthetized animals (Prys-Roberts et al., 1976). The presence of ISA may minimize the effect of adrenergic beta-receptor blockade in the case of hypercapnia and may prevent cardiovascular depression. To test this hypothesis, the effects of alterations of Pa_{CO_2} on the circulation have been studied before and after the administration of the non-selective adrenergic beta-receptor antagonist oxprenolol. The effects of oxprenolol on the systemic and coronary circulations were studied simultaneously, together with coronary sinus blood-gas tensions to gain more insight into the interaction between adrenergic beta-receptor blockade and carbon dioxide under anaesthesia.

METHODS

Ten unpremedicated dogs (mean weight 15.3 kg, SD 0.8) were studied. After induction of anaesthesia with thiopentone, 15 m kg^{-1} i.v. and endotracheal intubation, anaesthesia was maintained with 0.8–1.0% halothane in oxygen using constant volume intermittent positive pressure ventilation (tidal volume 40 ml kg^{-1}, rate 12 b.p.m.). Pa_{CO_2} was maintained at the required value by adding carbon dioxide to the inspired gas mixture and monitoring end-tidal carbon dioxide concentration with an infra-red analyser. The oesophageal temperature was monitored and maintained within the range of 36.5–37.5 °C by undertable heating. The e.c.g. was recorded. An i.v. infusion of fluid 5 ml kg^{-1} h^{-1} was given. The surgical preparation consisted of the insertion of a 20-cm Teflon catheter in the aortic arch via the left carotid artery followed by left lateral thoracotomy. Two electromagnetic flow transducers were implanted, one around the root of the aorta, the other around the left circumflex coronary artery. A miniature pressure transducer was inserted into the cavity of the left ventricle. Umbilical cannulae were inserted to the pulmonary artery, left atrium and coronary sinus. A pneumatic occluder was

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inserted around the left circumflex coronary artery to allow zero-flow oclusion.

The following variables were recorded: e.c.g., aortic pressure, left ventricular (LV) pressure, left atrial pressure, pulmonary arterial pressure, aortic flow and left circumflex coronary flow. Electronically derived signals included LV dP/dt, aortic blood acceleration and stroke volume. Details of the methods and calibrations have been given elsewhere (Burt and Foëx, 1979).

Arterial, mixed venous and coronary sinus blood samples were analysed at each stage of the experiment. Po_2, Pco_2 and pH were measured with electrode systems already described (Hahn, 1969, 1971). For determinations of Po_2, two electrodes were used; one for arterial samples was calibrated with room air and 60% oxygen; the other for mixed venous and coronary sinus blood samples was calibrated with pure nitrogen and 10% oxygen. Corrections for temperature difference were applied according to Kelman and Nunn (1966) and a blood–gas difference of 1.04 was applied for Po_2. Haemoglobin concentrations were determined by spectrophotometry.

Calculation

Systemic vascular resistance, left ventricular external work, peak left ventricular power and the rate–pressure product were computed as described previously (Burt and Foëx, 1979). Oxygen saturation was calculated using the dissociation curve of Rossing and Cain (1966). In the calculation of oxygen content, an oxygen combining capacity of 1.34 ml oxygen per gram of haemoglobin was used. Whole body oxygen consumption and myocardial oxygen consumption were calculated from the respective flows and arteriovenous oxygen content differences.

The results were analysed for statistical significance using paired Student's t test.

Experimental programme

Following surgical preparation, the animals were allowed to develop a steady cardiovascular state over a period of 1 h at an end-expiratory carbon dioxide concentration of 5.2%. After the steady state had been achieved, a dose–response curve to isoprenaline was constructed with the infusion rate doubled at each stage from an initial rate of 25 ng kg^{-1} min^{-1}. Twenty minutes after completion of the dose–response curve all variables had returned to steady state values; the haemodynamic variables were recorded and arterial, mixed venous and coronary sinus blood samples were withdrawn and immediately analysed. Hypocarbia was obtained by removing carbon dioxide from the inspired gas mixture. Recordings of the haemodynamic variables were taken after 20 min hypocarbia; at the same time blood samples were obtained. Carbon dioxide was then reintroduced and its concentration gradually increased over a period of 5 min to achieve an end-tidal concentration of about 10%. Recordings and blood samples were obtained after 20 min hypercarbia. A new normocarbic stage was obtained by reducing end-tidal carbon dioxide to 5.2% and values were found to be stable after 20 min. At normocarbia and after the appropriate recordings and blood samples had been taken, oxprenolol 0.3 mg kg^{-1} was injected i.v. and after 20 min, haemodynamic recordings and blood samples were obtained. The hypocarbic, hypercarbic and normocarbic stages were then repeated. A second dose–response curve to isoprenaline was constructed at normocarbia. At each stage, recordings were taken while respiration was halted (airway pressure 0 cm H_2O, lung volume at functional residual capacity). At the end of each experiment, the coronary artery flow transducer was calibrated by infusing measured volumes of blood into the left circumflex artery. The heart was removed and weighed.

RESULTS

The dose of oxprenolol chosen produced an eight-fold shift of the dose–response curve of heart rate to isoprenaline. The effects of alterations of Pa_{CO_2} on the haemodynamic values before and after adrenergic beta-receptor blockade are given in table I, while their effects on blood-gases are given in table II.

Effects of adrenergic beta-receptor blockade

At *normocarbia*, the effect of adrenergic beta-receptor blockade was a significant reduction of cardiac output by 9% caused by reduction of stroke volume while heart rate remained unchanged. After administration of oxprenolol, systemic vascular resistance (SVR) increased by 12.5%, while mean arterial pressure increased slightly. A significant but small (+0.9 mm Hg) increase of LVEDP was observed. All indices of

TABLE I. *Haemodynamic responses to alterations of Pa_{CO_2} before and after adrenergic beta-receptor blockade (oxprenolol 0.3 mg kg^{-1} i.v.) under halothane anaesthesia. Mean and SEM of 10 experiments. Significance (paired two-tailed Student's t test): *$P<0.05$, **$P<0.01$, ***$P<0.005$ for comparison between hypocapnia and respectively hypercapnia and normocapnia; †$P<0.05$ for comparison between normocapnic, hypocapnic or hypercapnic values before and after adrenergic beta-receptor blockade*

	Before beta-adrenergic blockade		
	Normocapnia	Hypocapnia	Hypercapnia
Heart rate (beat min^{-1})	127.0±8.0	131.0±8.0	141.0±7.0*
Stroke volume (ml)	15.3±1.3	14.6±1.5	15.8±1.7
Cardiac output (ml min^{-1} kg^{-1})	122.4±6.4	120.1±7.6	141.6±10.0*
Mean arterial pressure (mm Hg)	78.0±3.0	79.0±3.0	81.0±5.0
Systemic vascular resistance (dyne s cm^{-5})	3448.0±296.0	3587.0±286.0	3149.0±285.0
LVEDP (mm Hg)	2.8±0.4	2.7±0.5	5.4±0.6***
Peak aortic flow (ml s^{-1})	167.3±11.3	161.3±12.3	173.8±16.9
Aortic blood acceleration (ml s^{-2})	5660.0±415.0	5800.0±485.0	5760.0±485.0
LV d*P*/d*t* max (mm Hg s^{-1})	1850.0±105.0	1990.0±140.0	1840.0±105.0
(LV d*P*/d*t* max)/IP (s^{-1})	37.7±1.7	39.8±2.5	39.5±1.6
Peak LV power (mW)	2125.0±160.0	2060.0±180.0	2430.0±295.0
LV stroke work (mJ)	156.1±11.9	153.2±15.7	166.9±15.7
LV minute work (J)	19.2±1.0	19.4±1.5	23.2±1.9*
Coronary blood flow (ml min^{-1})	21.7±1.8	16.3±1.0***	35.0±5.0**
Mean pulm. art. pressure (mm Hg)	9.4±0.7	8.8±0.6	12.1±0.8**
Pressure–rate product (units × 10^{-3})	12.1±0.8	12.4±0.7	14.6±1.2***

	After beta-adrenergic blockade		
	Normocapnia	Hypocapnia	Hypercapnia
Heart rate (beat min^{-1})	128.0±7.0	125.0±9.0	131.0±6.0†
Stroke volume (ml)	13.9±1.5	14.7±1.9	14.7±1.5
Cardiac output (ml min^{-1} kg^{-1})	111.9±7.0†	111.6±7.1	124.0±11.1
Mean arterial pressure (mm Hg)	80.0±3.0	80.0±4.0	75.0±5.0
Systemic vascular resistance (dyne s cm^{-5})	3880.0±322.0	3828.0±207.0	3404.0±373.0
LVEDP (mm Hg)	3.7±0.5†	3.5±0.7	6.3±0.7***
Peak aortic flow (ml s^{-1})	160.4±14.2	166.9±18.1	162.4±15.3
Aortic blood acceleration (ml s^{-2})	5765.0±485.0	6190.0±695.0	5210.0±455.0
LV d*P*/d*t* max (mm Hg s^{-1})	1920.0±120.0	2120.0±205.0	1720.0±95.0*
(LV d*P*/d*t* max)/IP (s^{-1})	40.3±2.0	43.5±3.1	39.6±1.7
Peak LV power (mW)	2125.0±230.0	2240.0±315.0	2180.0±260.0
LV stroke work (mJ)	148.0±16.8	159.8±23.8	146.6±17.4†
LV minute work (J)	18.2±1.5	18.5±1.9	19.1±2.2†
Coronary blood flow (ml min^{-1})	20.5±1.5	16.4±1.3***	27.3±1.8***
Mean pulm. art. pressure (mm Hg)	9.3±0.5	9.2±0.5	12.8±0.8***
Pressure–rate product (units × 10^{-3})	12.6±0.8	12.1±1.0	13.2±1.0

myocardial performance were slightly increased after oxprenolol, but the differences ranged between 2% (aortic blood acceleration) and 7% (LV d*P*/d*t* max/IP) and did not reach statistical significance. Left ventricular peak power remained unchanged. Reductions of stroke work and minute work were similar to those of coronary flow (−5%) and paralleled the decline of myocardial oxygen consumption. With the exception of an 8% increase of the arterial to mixed venous oxygen content difference, blood-gases and oxygen transport appeared unaffected by oxprenolol.

At *hypocarbia*, adrenergic beta-receptor blockade was responsible for a small (5%) reduction of heart rate while stroke volume remained unchanged; thus cardiac output was slightly reduced. These changes were not significant. Systemic vascular resistance was increased by only 7% and left ventricular end-diastolic pressure by

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TABLE II. *Effect of alterations of* Pa_{CO_2} *on blood-gases and oxygen transport before and after adrenergic beta-receptor blockade (oxprenolol 0.3 mg kg^{-1} i.v.) under halothane anaesthesia. Mean and SEM of 10 experiments. Significance (paired two-tailed Student's* t *tests):* $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.005$ *for comparison between hypocapnia and respectively hypercapnia and normocapnia;* $^{\dagger}P<0.05$ *for comparison between normocapnic, hypocapnic or hypercapnic values before and after adrenergic beta-receptor blockade*

	Before beta-adrenergic blockade		
	Normocapnia	Hypocapnia	Hypercapnia
Pa_{O_2} (kPa)	57.2±3.9	62.0±3.6	53.8±3.2
Pa_{CO_2} (kPa)	5.5±0.2	2.9±0.2***	9.3±0.4***
pHa (units)	7.36±0.01	7.57±0.03***	7.15±0.02***
$P\bar{v}_{O_2}$ (kPa)	7.1±0.1	5.7±0.2***	9.1±0.4***
$P\bar{v}_{CO_2}$ (kPa)	6.5±0.1	3.8±0.3***	9.7±0.4***
pH$\bar{v}$ (units)	7 31±0.01	7.50±0.02***	7.15±0.02***
Pcs_{O_2} (kPa)	4.3±0.2	2.9±0.2***	6.4±0.4***
Pcs_{CO_2} (kPa)	7.2±0.2	4.1±0.3***	11.3±0.5***
pHcs (units)	7.31±0.01	7.52±0.02***	7.12±0.02***
Sa_{O_2} (%)	99.8±0.0	99.9±0.0	99.7±0.1
$S\bar{v}_{O_2}$ (%)	79.7±1.0	78.6±1.4	81.4±1.4
Scs_{O_2} (%)	51.5±2.8	41.6±3.0***	62.0±3.2*
Ca_{O_2} (ml dl^{-1})	19.8±0.6	20.0±0.6	19.7±0.6
$C\bar{v}_{O_2}$ (ml dl^{-1})	15.0±0.7	14.8±0.7	15.3±0.7
Ccs_{O_2} (ml dl^{-1})	9.7±0.7	7.8±0.7**	11.6±0.7*
$(Ca_{O_2}-C\bar{v}_{O_2})$ (ml dl^{-1})	4.9±0.2	5.2±0.3*	4.4±0.3
$\dot{V}o_2$ (ml min^{-1})	91.0±7.0	95.0±8.0	93.0±7.0
$(Ca_{O_2}-Ccs_{O_2})$ (ml dl^{-1})	10.2±0.6	12.2±0.7**	8.1±0.7*
$\dot{V}m_{O_2}$ (ml min^{-1})	2.3±0.4	2.0±0.3	2.7±0.3*

	After beta-adrenergic blockade		
	Normocapnia	Hypocapnia	Hypercapnia
Pa_{O_2} (kPa)	60.0±3.2	62.2±2.5	56.4±2.0
Pa_{CO_2} (kPa)	5.3±0.2	2.8±0.2***	9.2±0.3***
pHa (units)	7.34±0.01	7.53±0.03***	7.14±0.01***
$P\bar{v}_{O_2}$ (kPa)	6.9±0.2	5.6±0.2***	9.0±0.3***
$P\bar{v}_{CO_2}$ (kPa)	6.3±0.2	3.9±0.2***	9.5±0.3***
pH$\bar{v}$ (units)	7.3±0.01	7.47±0.02***†	7.14±0.02***
Pcs_{O_2} (kPa)	4.2±0.1	3.0±0.1***	6.3±0.2***
Pcs_{CO_2} (kPa)	6.9±0.3	4.1±0.3***	10.9±0.4***
pHcs (units)	7.3±0.02	7.49±0.02***†	7.12±0.02***
Sa_{O_2} (%)	99.8±0.0	99.9±0.0	99.7±0.0
$S\bar{v}_{O_2}$ (%)	77.6±1.0†	76.2±1.7†	80.8±1.2***
Scs_{O_2} (%)	50.5±1.9	41.6±2.2***	62.1±2.4***
Ca_{O_2} (ml dl^{-1})	19.9±0.7	19.9±0.7	19.8±0.6
$C\bar{v}_{O_2}$ (ml dl^{-1})	14.6±0.6	14.3±0.8	15.2±0.7**
Ccs_{O_2} (ml dl^{-1})	9.5±0.5	7.8±0.5***	11.7±0.7***
$(Ca_{O_2}-C\bar{v}_{O_2})$ (ml dl^{-1})	5.3±0.2†	5.6±0.3	4.5±0.2***
$\dot{V}o_2$ (ml min^{-1})	91.0±7.0	95.0±7.0	83.0±5.0
$(Ca_{O_2}-Ccs_{O_2})$ (ml dl^{-1})	10.5±0.5	12.1±0.5***	8.1±0.4***
$\dot{V}m_{O_2}$ (ml min^{-1})	2.1±0.3	2.0±0.3	2.3±0.2

0.8 mm Hg. All indices of myocardial performance (aortic blood acceleration (+7%), LV dP/dt (+6.5%), LV dP/dt max/IP (+10%)) were slightly enhanced after oxprenolol. Left ventricular peak power was increased by 9%. Coronary blood flow and myocardial oxygen consumption were unchanged. With the exception of an 8% increase of the arterial to mixed venous oxygen content difference, blood-gases and oxygen transport were unaffected by oxprenolol.

At *hypercarbia* both heart rate and stroke volume were reduced by approximately 7% after adrenergic beta-receptor blockade. Although relatively large, the 13% reduction of cardiac output did not reach statistical significance. Arterial pressure was slightly reduced after oxprenolol (−9%) while SVR was slightly increased (+8%). Left ventricular end-diastolic pressure was increased (+0.9 mm Hg) after adrenergic beta-receptor blockade. Aortic blood acceleration was reduced by 10% and LV dP/dt max by 6%, while LV dP/dt max/IP was unchanged, LV peak power was also reduced by 10%. Significant reductions of stroke work (−12%) and minute work (−18%) were observed, together with reductions of coronary flow (−20%). Myocardial oxygen consumption ($\dot{V}\text{m}_{\text{O}_2}$) was reduced by 14%. Since whole body oxygen consumption was reduced after oxprenolol, the arterial to mixed venous oxygen content difference remained unchanged, as did all blood-gas values.

Effect of carbon dioxide on coronary flow and on coronary sinus oxygen tension

Tables I and II describe the effect of carbon dioxide on systemic and coronary haemodynamics. While alterations in the systemic circulation caused by carbon dioxide were of relatively small magnitude both before and after administration of oxprenolol, large differences of coronary blood flow were observed (fig. 1). Before adrenergic beta-receptor blockade, hypocarbia caused a 24% reduction of coronary blood flow ($P < 0.005$) while hypercarbia caused a 59% increase of coronary blood flow ($P < 0.005$). These changes of coronary flow were accompanied by large and significant alterations of coronary sinus $P\text{O}_2$ (reduction by 1.4 kPa in response to hypercarbia, increase by 2.1 kPa in response to hypercarbia). The hypodynamic response of the circulation to hypocarbia is demonstrated by the reduction of $\dot{V}\text{m}_{\text{O}_2}$ while the hyperdynamic response of the circulation to hypercarbia is shown by the increase of $\dot{V}\text{m}_{\text{O}_2}$. However, the magnitude of the changes of $\dot{V}\text{m}_{\text{O}_2}$ (−11% and +16% respectively) was considerably smaller than that of the alterations of coronary blood flow. After adrenergic beta-receptor blockade, hypocarbia caused a 20% reduction of coronary blood flow ($P < 0.005$) while hypercarbia caused a 34% increase of coronary blood flow ($P < 0.005$). These changes were accompanied by a reduction in coronary sinus $P\text{O}_2$ ($P\text{cs}_{\text{O}_2}$) of −1.2 kPa with hypocarbia, and an increase in $P\text{cs}_{\text{O}_2}$ of 2.1 kPa with hypercarbia. These changes were highly significant. The hypodynamic response to hypocarbia was accompanied by a 6% reduction of $\dot{V}\text{m}_{\text{O}_2}$ and the modest hyperdynamic response to hypercarbia was accompanied by a 6% increase of $\dot{V}\text{m}_{\text{O}_2}$. Again, the alterations of $\dot{V}\text{m}_{\text{O}_2}$ were of small magnitude by comparison with the substantial alterations in coronary blood flow.

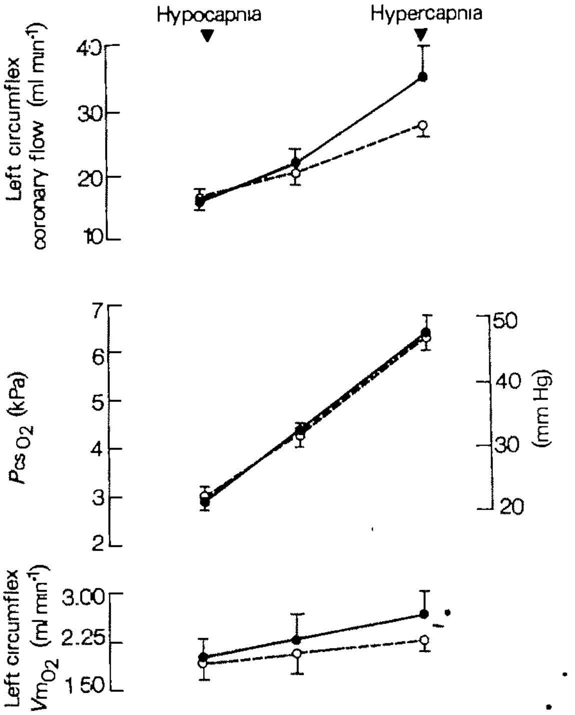

FIG. 1. The effects of hypocapnia and hypercapnia on left circumflex coronary blood flow, $P\text{cs}_{\text{O}_2}$ and $\dot{V}\text{m}_{\text{O}_2}$ studied in 10 dogs before (●——●) and after (○----○) oxprenolol 0.3 mg kg^{-1} i v Mean and SEM are given. Although the changes of coronary flow and of $P\text{cs}_{\text{O}_2}$ caused by carbon dioxide were all significant ($P < 0.001$), only the increase of $\dot{V}\text{m}_{\text{O}_2}$ with hypercapnia before oxprenolol was significant ($P < 0.05$) At the three $P\text{CO}_2$ concentrations none of the differences between values observed before and after oxprenolol was statistically significant

DISCUSSION

The effects of adrenergic beta-receptor antagonists on the circulation depend on the properties and dose of the drug and also on the preexisting level of sympathetic activity. The latter may be different in different experimental models, so that comparisons could be difficult. Comparisons are easier if the same experimental model, the same anaesthetic agent and equipotent doses of two or more beta-receptor antagonists are used. Halothane in oxygen was used to make such comparisons possible. Our own study of the effect of metoprolol (Burt and Foëx, 1979) fulfills these requirements and may be used for comparison, since both metoprolol 1 mg kg^{-1} and oxprenolol 0.3 mg kg^{-1} were used in doses producing an eight-fold shift to the right of the dose–response curve of heart rate to isoprenaline, 90 min after injection of the beta-blockers. At normocarbia, the effects of the cardioselective antagonist metoprolol were significant reductions of heart rate (−20%), arterial pressure (−10%), cardiac output (−21%) and all indices of myocardial performance (−32% for aortic blood acceleration, −31% for LV dP/dt max, −14% for LV dP/dt max/IP and −27% for LV peak power). Coronary blood flow was reduced by 25% and $\dot{V}m_{O_2}$ by 27%. All these changes were significant ($P<0.005$ except for heart rate for which P was <0.01). This significant reduction of myocardial performance accompanied by a substantial reduction of cardiac output, observed after metoprolol, is in contrast with the maintenance of cardiac performance after equipotent doses of oxprenolol. The only differences attaining statistical significance with oxprenolol were the reductions of cardiac output, and then by only 9% compared with 21% after metoprolol, and the modest increase in LVEDP, by 0.9 mm Hg, while the increase caused by metroprolol was by 1.5 mm Hg. All indices of performance significantly and substantially reduced by metoprolol were unchanged or enhanced after oxprenolol. Although performance was maintained or even enhanced, the small increase of SVR observed after oxprenolol caused a reduction of stroke volume. The differences between the responses to metoprolol and to oxprenolol tested under almost identical conditions and used in equipotent doses could be explained by two factors: cardioselectivity and presence of ISA. If cardioselectivity was the major factor, SVR would be expected to be increased more substantially after administration of the nonselective antagonist oxprenolol. This is not borne out by the experimental results: SVR increased by 13% after oxprenolol and by 15% after metoprolol. Thus the two agents had similar effects on vascular resistance. The differences between effects of equipotent doses of oxprenolol and metoprolol may be explained by intrinsic betasympathomimetic activity, a feature of the effect of oxprenolol. Nayler and Chang (1973) have shown that oxprenolol increases the tension developed by trabecular muscles isolated from the heart of control and of catecholamine-depleted dogs. Increases of contractile force and heart rate have also been observed in reserpinized dogs (Meier, 1970). In this study, administration of oxprenolol caused no change of heart rate and increased most indices of cardiac performance. This is not the usual pattern of response to adrenergic betareceptor blockade unless the agent exhibits partial agonist activity. Under anaesthesia, removal by oxprenolol of the small effect of adrenergic betareceptor activity on the cardiovascular system was accompanied by some stimulation of the betaadrenoceptors because of the intrinsic betasympathomimetic activity. The two effects cancelled out and oxprenolol appeared to have had little effect on the circulation at normocarbia.

At hypocarbia, the values for all indices of myocardial performance were also slightly increased after oxprenolol, but none of the haemodynamic values was significantly modified. This contrasts with observations made after administration of propanolol: using a dose that caused an eight-fold shift of the dose–response curve of heart rate to isoprenaline (Prys-Roberts et al., 1976) all indices of myocardial performance were decreased and heart rate significantly reduced (Foëx and Prys-Roberts, 1974). This would also indicate that the presence of intrinsic beta-mimetic activity may be advantageous. Because of the increased sympathetic activity of hypercarbia, the administration of betaadrenergic antagonists is likely to have a greater effect on the circulation at hypercarbia than at hypocarbia or at normocarbia. This was described with propranolol: cardiac output was substantially reduced (−34%), while heart rate was reduced by 14% and indices of left ventricular performance decreased by up to 40% (Foëx and Prys-Roberts, 1974). After oxprenolol, the only significant differences were 9% reduction of heart rate and reduction of left ventricular work (−12% for stroke work and −18% for minute work). Of the indices of cardiac performance, LV dP/dt max/IP was unaffected, while the other indices were reduced by up to 10%. Such changes were trivial by comparison with those caused by propranolol.

The hyperdynamic response to hypercapnia was decreased by oxprenolol (cardiac output increased only by 10% in response to hypercarbia instead of 16% before beta-adrenergic blockade), while it was inverted by propranolol (cardiac output decreased by 16% in response to hypercarbia instead of increasing by 24% before adrenergic beta-receptor blockade). The inversion of the response to hypercarbia after propranolol is a potential clinical hazard. Although normocarbia may easily be maintained during operation, this may not necessarily be so during the recovery period. Moreover, propranolol may in itself facilitate the development of hypercarbia by decreasing the sensitivity of the chemoreceptors to carbon dioxide (Mutschin et al., 1976). Oxprenolol does not cause inversion of the response of the circulation to hypercapnia. This difference between the effects of propranolol and those of oxprenolol, two non-selective beta-receptor antagonists, can only be attributed to the partial agonist characteristics of oxprenolol. This would reinforce the view that partial agonists may offer some advantages.

In this study, data concerning the effect of carbon dioxide on coronary blood flow are available. Consistent with observations made by other groups (Vance, Brown and Smith, 1973; Case, Greenberg and Moskowitz, 1975; Vance et al., 1979; Van den Bos, Drake and Noble, 1979), we have observed that hypocarbia caused significant reductions of coronary blood flow and of $P\text{cs}_{\text{O}_2}$ while the arterial to coronary sinus oxygen content differences increased. In response to hypercarbia, large increases of coronary blood flow and of coronary sinus oxygen tension were observed while the arterial to coronary sinus oxygen content difference decreased. After adrenergic beta-receptor blockade with oxprenolol, the effects of hypocarbia on coronary blood flow, arterial to coronary sinus oxygen content difference, $P\text{cs}_{\text{O}_2}$ and $\dot{V}\text{m}_{\text{O}_2}$ were essentially the same as before blockade. The effect of hypercarbia on coronary blood flow was minimized by adrenergic beta-receptor blockade. However, an increase of coronary blood flow by 34% accompanied by an increase in $\dot{V}\text{m}_{\text{O}_2}$ of only 5% indicates that carbon dioxide caused coronary vasodilatation even though the adrenergic beta-receptors were blocked. Case and his colleagues (1978) have used propranolol in a few of their experiments and observed that hypercarbia caused coronary vasodilatation even in the presence of beta-adrenergic receptor blockade. Van den Bos, Drake and Noble (1979) found no increase of coronary blood flow in response to hypercapnia after administration of sotalol. However, in their study there was, surprisingly, no increase of coronary blood flow, even in the absence of beta-adrenergic receptor blockade in the range of $P\text{CO}_2$ 3–11 kPa. Our data suggest that, within this range, carbon dioxide causes coronary vasodilatation irrespective of the integrity of beta-adrenergic mechanisms.

The possible clinical implications of this study are three-fold. First, the effect of oxprenolol on the circulation appears to be of small magnitude and the response to hypercarbia is not inverted; such findings suggest that intrinsic sympathomimetic activity could be of clinical significance. Second, the carbon dioxide-induced alterations of coronary blood flow do not appear to be mediated by beta-adrenergic mechanisms; third, hypocarbia with or without adrenergic beta-receptor blockade is capable of severely reducing coronary blood flow and $P\text{cs}_{\text{O}_2}$, indicating reduced myocardial oxygen availability.

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INTERACTIONS DU BLOCAGE ADRENERGIQUE DU RECEPTEUR BETA (OXPRENOLOL) ET DE LA Pco_2 SUR UN CHIEN ANESTHESIE: INFLUENCE DE L'ACTIVITE SYMPATHOMIMETIQUE BETA INTRINSEQUE

RESUME

On a étudié sur 10 chiens, dont la poitrine était ouverte et les poumons ventilés avec de l'halothane à 0,8% dans de l'oxygène, les effets de la variation de la Pa_{CO_2} sur l'hémodynamique coronaire et systémique et sur les gaz et le sang du sinus coronaire, avant et après l'administration par voie intraveineuse d'oxprénolol à raison de 0,3 mg kg^{-1}. La réaction hyperdynamique de la circulation à hypercapnie n'a été réduite que marginalement après l'administration d'oxprénolol (le débit cardiaque a augmenté de 10%—par opposition à 16% avant l'administration d'oxprénolol) Avant et après l'administration d'oxprénolol, l'hypocapnie a entraîné de fortes diminutions du débit sangin coronaire (−24% et −20% respectivement), alors que l'hypercapnie a causé de fortes augmentations du débit sanguin coronaire (+59% et +34% respectivement). L'oxprénolol ne semble pas modifier d'une manière significative la réaction circulatoire aux modifications de la tension du gaz carbonique artériel.

WECHSELWIRKUNGEN ZWISCHEN ADRENERGISCHER BETA-REZEPTORBLOCKIERUNG (OXPRENOLOL) UND Pco_2 BEIM NARKOTISIERTEN HUND: EINFLUSS DER SPEZIFISCH SYMPATHIKOMIMETISCHEN AKTIVITÄT

ZUSAMMENFASSUNG

Wirkungen einer Veranderung von Pa_{CO_2} auf systemische und Koronarhamodynamik und auf Koronar-Sinusblutgase wurden im geöffneten Brustraum von 10 Hunden studiert, deren Lungen mit 0,8% Halothan in Sauerstoff beluftet wurden—vor und nach intravenoser Verabreichung von 0,3 mg kg^{-1} Oxprenolol. Die hyperdynamische Reaktion des Kreislaufs auf Hyperkapnie war darauf nur sehr schwach reduziert (Herzminutenvolumen stieg um 10% im Gegensatz zu 16% vor Oxprenolol). Vor und nach der Droge wurde der Koronarblutfluss durch Hypokapnie stark reduziert (−24%, bezw. −20%), während er durch Hyperkapnie stark erhoht wurde (+59%, bezw. +34%). Oxprenolol scheint die Kreislaufreaktion nicht wesentlich zu beeinflussen, was Änderungen der arteriellen Kohlendioxydspannung betrifft.

INTERACCIONES ENTRE EL Pco_2 Y EL RECEPTOR BETA ADRENERGICO DE BLOQUEO (OXPRENOLOL) EN EL PERRO ANESTESIADO: INFLUENCIA DE LA ACTIVIDAD BETA SIMPATOMIMETICA INTRINSECA

SUMARIO

Se estudiaron los efectos del cambio en Pa_{CO_2} en las hemodinámicas sistémicas y coronarias, y en los gases sanguíneos de las cavidades coronarias en 10 perros a pecho albierto, en los que los pulmones se ventilaron con oxígeno al 0,8% de halotano, antes y después de la administración de 0,3 mg kg^{-1} de oxprenolol intravenoso. La respuesta hiperdinámica a la hipercapnia se redujo tan sólo de forma parcial después del oxprenolol (la producción cardíaca aumentó en un 10% en oposición a un 16% antes del oxprenolol). Antes y después del oxprenolol, la hipocapnia ocasionó grandes reducciones del flujo sanguíneo coronario (−24% y −20% respectivamente), al tiempo que la hipercapnia ocasionó grandes incrementos de dicho flujo (+59% y +34% respectivamente) El oxprenolol no parece modificar de forma significativa la respuesta circulatoria a las variaciones de dióxido de carbono en la tensión arterial

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PHARMACOKINETICS AND ANALGESIC EFFECT OF KETAMINE IN MAN

J. A. CLEMENTS AND W. S. NIMMO

SUMMARY

The pharmacokinetics and analgesic effect of i.v. ketamine in doses of 125 μg kg^{-1} and 250 μg kg^{-1} were determined in five healthy volunteers. Analgesia was measured with the submaximal effort tourniquet test. Both doses of ketamine prolonged the period of pain-free ischaemic exercise while the plasma ketamine concentration was greater than 100 ng ml^{-1}. Ketamine was distributed rapidly ($T_{\frac{1}{2}}^{\alpha}$=17 min). The elimination half-life was 186 min.

Ketamine (2-o-chlorophenyl-2-methylamino-cyclohexanone) rapidly produces sleep following i.v. injection of 1–2 mg kg^{-1}(Ghoneim and Korttila, 1977). It has analgesic properties (Caro, 1974; Wilson, Herrin and Richey, 1978) and has been used as repeated i.v. injections of 0.5 mg kg^{-1} or as an infusion of 1–2 mg min^{-1} to provide analgesia after operation (Ito and Ichiyanagi, 1974; Clausen, Sinclair and Hasselt, 1975; Austin, 1976).

We have investigated the pharmacokinetics and analgesic activity of i.v. ketamine at two dose concentrations.

METHODS

Five fasting healthy adult males (age 33.8 ± 1.4 yr, (SEM) height 1.83 ± 0.02 m, weight 74.8 ± 2.1 kg) were studied on three occasions at least 1 week apart: once after ketamine 250 μg kg^{-1}, once after ketamine 125 μg kg^{-1} and once after a placebo injection of saline. The order was randomized and the test injection was given i.v. to the antecubital vein over a period of 15 s. Neither the subject nor the person recording the pain score was aware of the nature of the injection. Blood samples were taken from a venous cannula distal to the injection site in the dominant arm at intervals for 7 h. Plasma was separated and analysed for ketamine and its two metabolites by gas-liquid chromatography.

Analgesia

The method used was similar to that of Harrison and Bigelow (1943). With the subject supine, a sphygmomanometer cuff on the non-dominant arm was inflated to 250 mm Hg and the subject was required to squeeze a rubber ball once per second. At 15-s intervals he was asked to describe pain in the forearm as none, mild, moderate or severe. When the pain became intolerable, the sphygmomanometer cuff was immediately deflated and the "tourniquet time" noted. Subjects were tested at 5-min intervals for a 30-min control period. Ketamine (Ketalar, Parke Davis) or saline was then injected and the subject tested at 5-min intervals for 20 min and then at 10-min intervals for a further 40 min. Tests of statistical significance were carried out by paired *t* test.

Ketamine analysis

Plasma samples were analysed for ketamine, norketamine (metabolite I) and dehydronorketamine (metabolite II) as their heptafluorobutyryl derivatives using a gas–liquid chromatograph with electron-capture detection (Walle and Ehrsson, 1970; Chang and Glazko, 1972).

The extraction and derivatization procedure was that of Chang and Glazko (1972) with the following modifications. Toluene was used as the solvent; derivatization was carried out using pyridine 20 μlitre and heptafluorobutyric anhydride 20 μlitre and by heating for 10 min at 40 °C. Oven temperature was maintained at 195 °C. The electron capture detector (nickel-63 source) was set at a pulse frequency of 6 kHz and operated at 250 °C. The internal standard was 2-o-bromophenyl-2-methylaminocyclohexanone hydrochloride. Peak height ratio (analyte : internal standard) was proportional to the concentration in plasma for ketamine in the range 20–200 ng ml^{-1} and for metabolites I and II in the range 10–100 ng ml^{-1}. The

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coefficients of variation for replicate analyses ($n = 5$) on standard solutions were 5.3% (concentration 50 ng ml^{-1}) for ketamine and 7.4% (concentration 500 ng ml^{-1}) for metabolite I.

After mixing the internal standard solution (1.0 ml) and the plasma sample (1.0 ml), the solution was carried through the assay procedure. The concentrations were calculated from peak height ratios with reference to standard solutions run on the same day. All plasma samples were analysed in duplicate.

RESULTS

Pain measurements

Ketamine prolonged the period of pain-free ischaemic exercise as shown by the pain scores at 15-s intervals (fig. 1) and by the "tourniquet times" (table I). In the 30-min period before injection the "tourniquet times" did not differ significantly from one another and the pain scores were the same in all three groups; moderate to severe pain was experienced within 60 s of inflation of the cuff. Immediately after the administration of

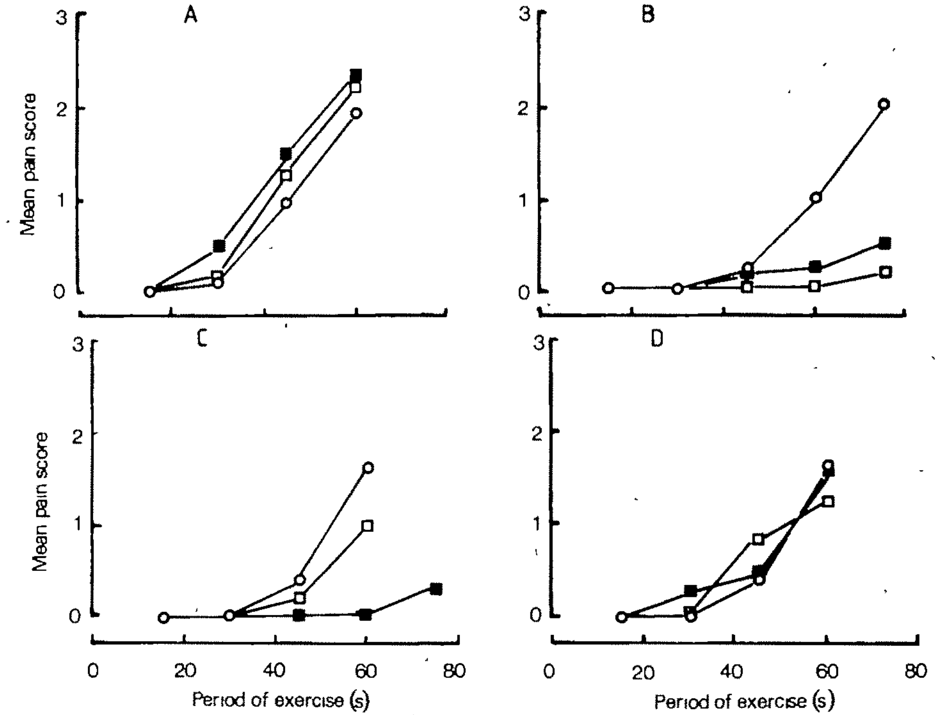

FIG 1. The effect of ketamine on pain of ischaemic exercise in five subjects. A = before drug; B = 0 min; C = 5 min, D = 10 min. Pain scores: 0 = no pain; 1 = mild pain; 2 = moderate pain; 3 = severe pain. ○—○ = Control; □—□ = ketamine 125 µg kg^{-1}, ■—■ = ketamine 250 µg kg^{-1}.

TABLE I *Times to reach intolerable pain during ischaemic exercise of the arm ("tourniquet times"). Mean times* ±SEM (*s*). *n.s. = Not significantly different from control times before injection.* * *Significantly greater than times before injection* (P *<0.05*)

Study	Before injection	Time after injection			
		0	5 min	10 min	15 min
Control	81.4±6.0	89.2±5.6	84.6±5.4	86.8±8.5	87.0±8.3
Ketamine 250 µg kg^{-1}	75.8±7.9 n.s.	106 ±13*	105 ±23*	75.2±4.0	74.4±5.4
Ketamine 125 µg kg^{-1}	74.4±5.1 n.s.	94.2±4.3*	76.6±6.6	73.6±4.3	69.8±3.6

either dose of ketamine and also at 5 min after the larger dose, the pain was graded as none to mild at 75 s. Similarly, immediately after both doses of ketamine and also 5 min after the larger dose, the "tourniquet time" was significantly prolonged. At other times and following placebo injection, pain scores and "tourniquet times" were similar to those recorded in the period before injection. Thus the analgesia produced by ketamine 250 µg kg^{-1} i.v. lasted more than 5 min while that produced by 125 µg kg^{-1} lasted less than 5 min.

Pharmacokinetics

Plasma ketamine concentration–time data were fitted satisfactorily by a two-compartment open model by non-linear regression analysis (Clements and Prescott, 1976). Typical results in one subject are given in figure 2. There were no significant differences in any of the pharmacokinetic parameters following either dose (table II). The mean terminal plasma half-life was about 3 h and the total body clearance was 17 ml min^{-1} kg^{-1}. Plasma concentrations of norketamine increased rapidly and reached a mean peak concentration of 40 ± 14 ng ml^{-1}(± SEM) at 75 min and 21 ± 3 ng ml^{-1} at 45 min after the larger and smaller dose respectively. No dehydronorketamine was detected in plasma samples in the study; if present, the concentration was less than the limit of detection of 50 ng ml^{-1}.

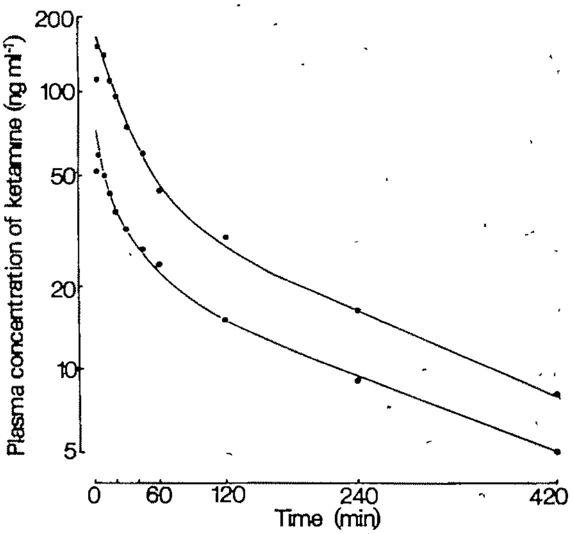

FIG. 2. Plasma concentrations of ketamine following i.v. injection of 125 µg kg^{-1} (○——○) (lower trace) and 250 µg kg^{-1} (●——●) (upper trace) in one subject.

TABLE II. *Pharmacokinetic values (mean* ± SEM) *for ketamine after i.v. bolus injection of 250* µg kg^{-1} *or 125* µg kg^{-1}(n = 5)

Value	250 µg kg^{-1}	125 µg kg^{-1}
A_1 (ng ml^{-1})	108 ± 14	82 ± 12
A_2 (ng ml^{-1})	39 ± 2	22 ± 1
α (min^{-1})	0.0394 ± 0.0029	0.0443 ± 0.0014
β (min^{-1})	0.0038 ± 0.0002	0.0039 ± 0.0004
V^{β} (litre kg^{-1})	5.1 ± 0.3	4.2 ± 0.2
V^{ss} (litre kg^{-1})	3.1 ± 0.4	2.1 ± 0.3
Clearance (ml min^{-1} kg^{-1})	19.1 ± 1.1	16.3 ± 1.3

DISCUSSION

Previous studies of ketamine in patients have been performed with infusions (Ito and Ichiyanagi, 1974; Clausen, Sinclair and Hasselt, 1975) and there is little information on the duration of action of a single analgesic dose of the drug. In our study a single injection of 250 µg kg^{-1} increased the pain threshold for more than 5 min at a time when the plasma ketamine concentration was greater than 100 ng ml^{-1}.

The early rapid disposition of ketamine with a mean half-life of 17 min is consistent with a high oil : water partition coefficient (Cohen and Trevor, 1974) and extensive distribution within the body (White et al., 1976). The pharmacokinetic values following the smaller and larger doses did not differ significantly, suggesting that disposition of ketamine is not dose-dependent in this range. The pharmacokinetics of ketamine in analgesic doses have not been reported previously.

In patients receiving an anaesthetic dose of ketamine, plasma half-lives of 17 min and more than 4 h have been reported for the fast (α phase) and slow (β phase) disposition phases respectively (Chang et al., 1970; Chang and Glazko, 1972). A plasma half-life of 79 min has recently been reported in patients who had received an i.v. infusion (Idvall et al., 1979). In a study of five anaesthetized patients receiving ketamine 2.5 mg kg^{-1}, the plasma concentration–time data fitted a two-compartment open model; the mean disposition half-lives of 11 min and 151 min (Wieber et al., 1975) are in good agreement with the values in our study (17 min and 186 min respectively). In addition, the values of the apparent volume of distribution (214 litre) and total body clearance (1.23 litre min^{-1}) were similar to the values obtained in our study (347 litre and 1.32 litre min^{-1} respectively). This suggests that the pharmacokinetics of ketamine are not markedly altered by the dose over a 20-fold range.

In patients receiving ketamine 2.2 mg kg^{-1}, consciousness returned 9–20 min after the i.v. injection when plasma concentrations were in the range 700–1120 ng ml^{-1} (Little et al., 1972). After i.v. infusion, consciousness returned when plasma concentration was less than 640 ng ml^{-1} (Idvall et al., 1979). It appears that the analgesic effect of ketamine occurs at much lower concentrations than the anaesthetic effects.

ACKNOWLEDGEMENTS

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PHARMACOCINETIQUE ET EFFET ANALGESIQUE DE LA KETAMINE CHEZ L'HOMME

RESUME

La pharmacocinétique et les effets analgésiques de l'administration de kétamine par voie intraveineuse en doses de 125 µg kg^{-1} et de 250 µg kg^{-1} ont eté determines sur cinq volontaires en bonne santé L'analgésie a été mesurée à l'aide de l'essai du tourniquet à effort submaximal. Les deux doses de kétamine ont prolongé la periode d'exercice ischémique sans douleur alors que la concentration de kétamine dans le plasma était supérieure à 100 ng ml^{-1}. La kétamine s'est répartie rapidement ($T_{\frac{1}{2}}{}^{\alpha}$ = 17 min) La demi-vie d'élimination a été de 186 min.

PHARMAKOKINETISCHE UND ANALGETISCHE WIRKUNG VON KETAMIN BEIM MENSCHEN

ZUSAMMENFASSUNG

Besagte Ketamin-Wirkung von intravenosen Dosen zu 125 µg kg^{-1} und 250 µg kg^{-1} wurde bei funf gesunden Freiwilligen untersucht. Die schmerzlindernde Wirkung wurde mit dem untermaximalen Knebelwirkungstest gemessen Beide Ketamin-Dosen verlängerten die Periode der schmerzfreien ischamischen Übung, wahrend die Ketamin-Plasmakonzentration uber 100 ng ml^{-1} lag Ketamin wurde rapide verteilt ($T_{\frac{1}{2}}{}^{\alpha}$ = 17 min). Die Ausscheidungs-Halbwertszeit betrug 186 Minuten

EFECTOS FARMACOCINETICOS Y ANALGESICOS DE LA KETAMINA EN EL HOMBRE

SUMARIO

Se determinaron en cinco voluntarios sanos los efectos farmacocinéticos y analgésicos de la ketamina intravenosa, en dosis de 125 µg kg^{-1} y de 250 µg kg^{-1} La analgesia se midio con la de torniquete de esfuerzo supramáximo Ambas dosis de ketamina prolongaron el periodo isquémico sin dolor, mientras que la concentración de ketamina en el plasma fue superior a 100 ng ml^{-1}. La ketamina se distribuyó rápidamente ($T_{\frac{1}{2}}{}^{\alpha}$ = 17 min). El periodo de vida media para la eliminación fue de 186 min

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THE PHARMACOLOGY OF ATRACURIUM: A NEW COMPETITIVE NEUROMUSCULAR BLOCKING AGENT

R. HUGHES AND D. J. CHAPPLE

SUMMARY

Atracurium besylate, 2,2'-(3,11-dioxo-4,10-dioxatridecylene)-bis-[6,7-dimethoxy-1-(3,4-dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinolinium] dibenzenesulphonate, is one of a new series of competitive neuromuscular blocking agents. An i.v. dose of 0.25 mg kg^{-1} produced complete paralysis in anaesthetized cats, dogs and rhesus monkeys; paralysis was of medium duration and was readily antagonized by neostigmine. Vagal blockade occurred only after doses 8–16 times greater than the full neuromuscular paralysing dose and effects on sympathetic mechanisms were minimal. Hypotension and bradycardia were evident after supramaximal doses of 4 mg kg^{-1} i.v. and these effects, together with circulatory depression, were probably attributable to histamine release. *In vitro* studies have shown that the non-enzymic decomposition of atracurium by "Hofmann Elimination" was enhanced by increasing pH. *In vivo* neuromuscular paralysis was significantly reduced when the arterial pH was increased. There were indications that neither the liver nor the kidney plays a major role in the metabolism and elimination of unchanged drug. These results are of sufficient interest to merit the evaluation of atracurium in anaesthetized man.

All competitive neuromuscular blocking agents currently in general use, in addition to their actions at the neuromuscular junction, inhibit cholinergic transmission at autonomic sites and may produce undesirable cardiovascular side-effects (Hughes and Chapple, 1976a). Furthermore, all show a significant increase in the duration of neuromuscular blockade when excretion is inhibited by renal insufficiency (Wingard and Cook, 1977). Atracurium besylate, 2,2'-(3,11-dioxo-4,10-dioxatridecylene)-bis-[6,7-dimethoxy-1-(3,4-dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinolinium] dibenzenesulphonate, is one of a new series of neuromuscular blocking agents, which has been developed in an attempt to overcome the disadvantages of such drugs (Stenlake, 1979).

The chemical structure of atracurium is shown in figure 1 and the arrows indicate the likely metabolic pathways. These are (1) an enzymic ester hydrolysis to give the monoquaternary metabolites and (2) decomposition by what is called "Hofmann Elimination". Under mild alkaline conditions fission occurs at the quaternary nitrogen to give laudanosine as the main metabolite (Stenlake, 1979). No other available neuromuscular blocking agent undergoes this kind of breakdown at physiological pH. Moreover, we have verified that the metabolites from both potential metabolic pathways are without neuromuscular and cardiovascular effects in amounts greatly in excess of those likely to be present after neuromuscular blocking doses of atracurium (Hughes and Chapple, 1978).

We now report in detail the pharmacology of atracurium in laboratory animals, and a comparison with known drugs, in order to assess the clinical potential of this agent. A preliminary account of this work has been presented to the Anaesthetic Research Society (Hughes and Chapple, 1980).

METHODS

Nerve–muscle preparations

Isolated chick biventer-cervicis preparations were set up in Krebs solution at 35 °C and equilibrated with 95% oxygen and 5% carbon dioxide. The nerve was stimulated at 0.12 Hz with rectangular pulses of supramaximal voltage and duration and the muscle responses were recorded on a smoked drum.

Cats of either sex weighing 2.6–3.7 kg were studied after anaesthesia had been induced with 2–5% halothane and maintained with chloralose 60–80 mg kg^{-1} i.v. and sodium pentobarbitone 18–24 mg kg^{-1} i.v. after cannulation of a jugular

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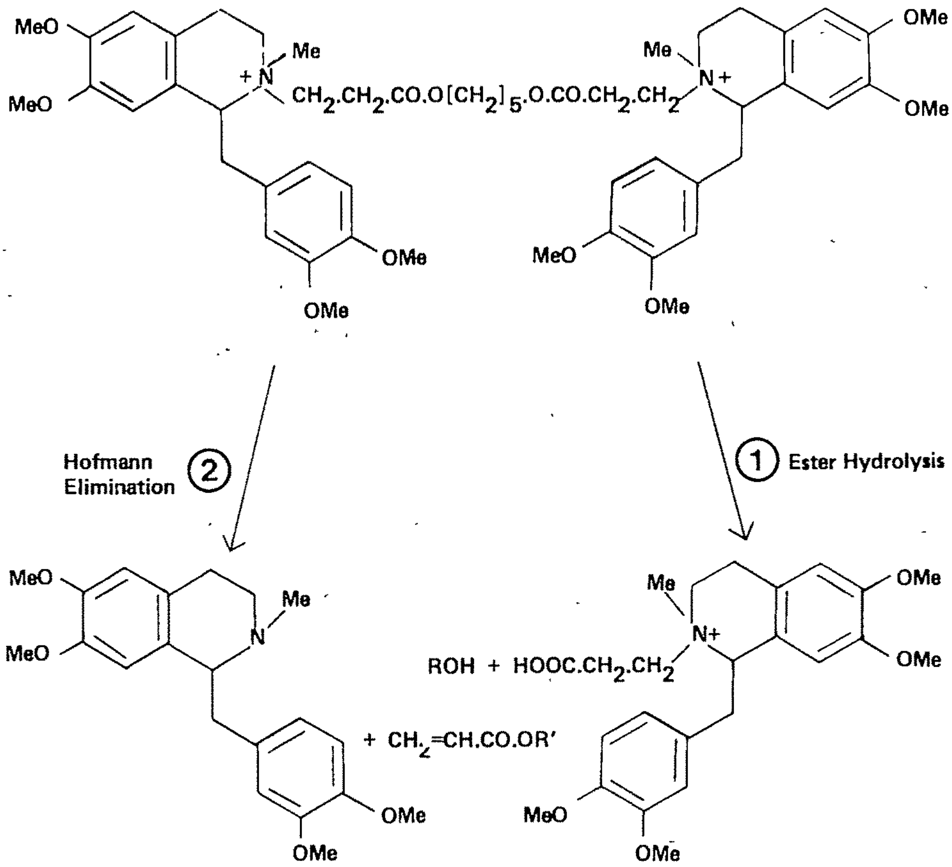

FIG. 1. Chemical structure of atracurium; the arrows indicate the likely metabolic pathways.

vein as described previously (Hughes and Chapple, 1976a). The twitch responses of the right gastrocnemius muscle were elicited by stimulation of the sciatic nerve at a frequency of 0.1 Hz with rectangular pulses of supramaximal voltage and 0.1–0.15 ms duration. In most experiments the left gastrocnemius muscle was stimulated indirectly with tetanic pulses of 30–35 Hz for 1 s every 10 s. Arterial pressure was measured from the carotid artery and breathing was monitored with a thermistor placed inside a tracheal cannula. The electrocardiogram was recorded from chest leads and heart rate from a cardiotachometer. Simultaneously, effects on autonomic mechanisms were assessed by stimulating at the cervical vagus nerve for 10 s at 10–20 Hz, and measuring the ensuing bradycardia (parasympathetic), and the cervical sympathetic nerve for 60 s and recording the induced contractions of the nictitating membrane. Oesophageal temperature was measured with a probe and maintained at 36–37 °C. Similar techniques were used on beagle dogs of either sex weighing 8.6–14.9 kg and analogous procedures were carried out using rhesus monkeys of 2.8–4.1 kg as described by Hughes and Chapple (1976b). In monkeys anaesthesia was induced with thiopentone 25 mg kg^{-1} i.v. and maintained with 50% nitrous oxide in oxygen supplemented by thiopentone 5–12 mg kg^{-1} i.v. when required. Effects on sympathetic mechanisms were investigated by measuring the vasopressor response to carotid occlusion for 10 s. During neuromuscular paralysis ventilation of the lungs of the cats and dogs was with air using a Starling Ideal pump and of the rhesus monkeys with nitrous oxide and oxygen using a Phillips AV1 Ventilator.

Interaction with halothane

Initially, dose–response curves for neuromuscular blockade of the single twitch response of the gastrocnemius muscle by atracurium were established in cats anaesthetized with chloralose followed 60–90 min later by inhalation of concentrations of 1 or 2% halothane. The same doses were then repeated 30–60 min after beginning the administration of halothane. A cross-over design was adopted in which the sequence of administration was reversed. In half the cats used, the control dose–response curves for atracurium followed 120 min after the interaction study with halothane.

Cholinesterase inhibition

The enzyme was extracted from human skeletal muscle and prepared as a suspension in phosphate buffer at pH 8. Enzymic activity was measured as described by Ellman and others (1961) using acetylthiocholine 0.5 mmol litre^{-1} as substrate. Each drug was tested at a range of concentrations and the results expressed as the concentration causing 50% reduction in the rate of hydrolysis of substrate compared with the non-inhibited controls (IC_{50}).

Haemodynamic studies

These were carried out on open-chest beagle dogs anaesthetized with chloralose using techniques described in detail elsewhere (Hughes, 1971). An electromagnetic flow sensor was placed around the root of the ascending aorta to record aortic blood flow and a stiff polyethylene catheter inserted down the left carotid artery to measure aortic pressure. The flow signal was integrated to obtain cardiac output (less coronary flow) and differentiated to derive maximum acceleration (an index of myocardial contractility). Peripheral vascular resistance was computed by dividing mean aortic pressure by mean aortic flow.

Inotropic and chronotropic effects were assesed using guineapig atria preparations set up at 35 °C in modified Ringer Z solution bubbled with 95% oxygen and 5% carbon dioxide. The force and frequency of each contraction were recorded with a displacement transducer.

Histamine release

Histamine release was studied in beagle dogs anaesthetized with chloralose. Initially, effects of atracurium, tubocurarine (for comparison) and histamine on carotid pressure were established in each dog. I.v. injections of 10 mg kg^{-1} of the H_1-receptor antagonist mepyramine and 15 mg kg^{-1} of the H_2-receptor antagonist burimamide or cimetidine were then given, followed by histamine to ascertain that its vasodepressor response was blocked. The established doses of atracurium and tubocurarine were repeated to determine their effects on carotid pressure during histamine-receptor blockade.

Changes in acid–base balance

Effects of respiratory and metabolic acidosis and alkalosis on neuromuscular blockade of the tetanic and single twitch responses of the gastrocnemius muscles by atracurium were investigated in groups of cats anaesthetized with chloralose using techniques described previously (Hughes, 1970). Arterial blood was sampled frequently for measurement of pH, $P\text{CO}_2$ and $P\text{O}_2$. Controlled ventilation was used throughout. I.v. doses of atracurium were given before, during and after the imposed changes in acid–base balance; intervals of 45–85 min were allowed between doses.

Elimination of atracurium

A cannula was placed in a branch of the hepatic portal vein of anaesthetized cats so that atracurium could be administered through the liver. A cross-over design was adopted so that half the cats first received increasing doses of atracurium through the hepatic portal vein, after which dose–response curves were obtained for neuromuscular blockade of the single twitch response of the gastrocnemius muscle. After an interval of 120 min from the last dose, when recovery was complete, the same sequence of doses was given through the jugular vein and dose–response curves established for this route; in the other cats the order of administration was reversed.

In other tests, increasing doses of atracurium or gallamine (for comparison) were given to anaesthetized cats to establish dose–response curves for neuromuscular blockade. After an interval of 60 min from the last dose, when recovery was complete, renal function was abolished by ligating the renal artery and vein and ureter of each kidney. Sixty minutes later administration of the same range of doses of atracurium and gallamine was repeated to obtain dose–response curves in the absence of renal function.

Drugs

Solutions of drugs were made in NaCl 9 mg ml^{-1} and those of atracurium were acidified by addition of one drop of acetic acid 2 mol litre^{-1} to 2–4 ml of solution to maintain pH in the optimum range of stability. Doses stated are those of the dibesylate salt of atracurium, the dibromide of dimethyltubocurarine, fazadinium and pancuronium, the chloride of edrophonium and acetylthiocholine, the dichloride of alcuronium, suxamethonium and tubocurarine, the di-iodide of decamethonium, the hydrochloride of cimetidine, the tri-ethiodide of gallamine, the maleate of mepyramine, the methylsulphate of neostigmine, the acid phosphate of histamine, the sulphate of physostigmine. A solution of burimamide was obtained by suspending the drug in 0.9% sodium chloride and acidifying with a minimal volume of HCl 1 mol litre^{-1}.

Analysis of results

Statistical analysis was with Student's *t*-tests.

RESULTS

Neuromuscular studies

Bath concentrations of atracurium 0.5–1.0 µg ml^{-1}, like those of other competitive agents tubocurarine (0.5–1.0 µg ml^{-1}) and gallamine (10 µg ml^{-1}), caused blockade of the isolated chick biventer-cervicis preparation without producing an initial contracture. The block was antagonized by physostigmine 2 µg ml^{-1} and edrophonium 2 µg ml^{-1} and reversed by washing out the bath medium and refilling with fresh Krebs solution. In contrast the blocking action of the depolarizing drugs, suxamethonium 0.1 µg ml^{-1} and decamethonium 0.05 µg ml^{-1}, was preceded by an initial contracture. Blockade was potentiated by edrophonium but reversed by washing out.

In anaesthetized cats, i.v. doses of atracurium 0.25 mg kg^{-1} were sufficient to cause complete neuromuscular blockade of the single twitch and tetanic responses of the gastrocnemius muscle and to arrest breathing (fig. 2). The results in cats, and those in dogs and rhesus monkeys, are summarized in table I. The dose estimated to produce 50% paralysis shows that, for each species studied, the tetanic response was significantly more sensitive to

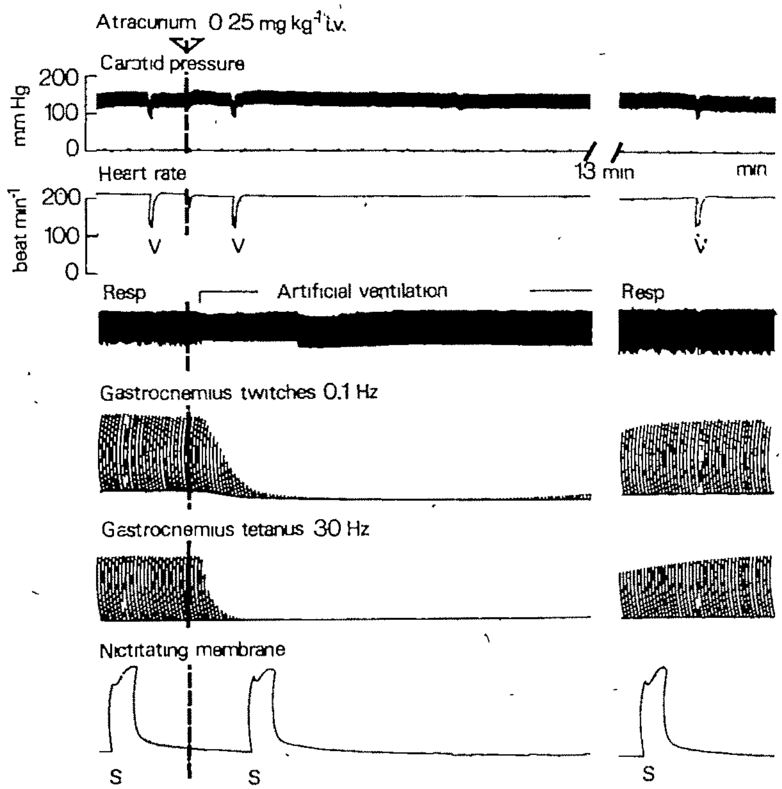

FIG. 2. Tracing from a cat anaesthetized with chloralose. A dose of atracurium 0.25 mg kg^{-1} i.v. arrested breathing and abolished the single twitch and tetanic responses (30 Hz) of the gastrocnemius muscle to indirect stimulation. Effects on carotid arterial pressure, heart rate, vagal-induced bradycardia and contractions of the nictitating membrane in response to sympathetic nerve stimulation were minimal. S = sympathetic nerve stimulation, 10 Hz. V = vagal nerve stimulation, 10 Hz.

TABLE I. *Neuromuscular blocking effects of atracurium in groups of anaesthetized cats, dogs and rhesus monkeys. Maximal block of the single twitches and the tetanic contractions (30 Hz for 1 s) is expressed as a percentage of initial value. Mean values are quoted (± SEM where relevant). Asterisks denote that potency in dogs was significantly different from that in cats and rhesus monkeys at the 1% level (**). †One result only*

Species	Dose i.v. (mg kg^{-1})	Single twitch			Tetanic response (30 Hz)			50% paralysing dose (mg kg^{-1} i.v.)	
		% Block	Onset max effect (min)	Full recovery (min)	% Block	Onset max effect (min)	Full recovery (min)	Single twitch	Tetanic response
Cats	0.0625	0	0	0	3†	2†	5†		
($n = 6$)	0.125	54±12.9	5.0±0.7	11±2.2	93±3.2	5.9±1.0	21±1.4		
	0.25	99±1.43	3.0±0.8	29±2.5	100	2.1±0.5	37±2.0		
	0.5	100	0.9±0.05	45±4.1	100	0.5±0.04	51±3.5	0.129	0.095
	1.0	100	0.5±0.04	61±6.2	100	0.4±0.06	65±4.1	±0.008	±0.005
	2.0	100	2.2±1.8	80±5.5	100	0.4±0.06	85±5.5	$P<0.01$	
	4.0	100	0.8±0.4	>80	100	0.3±0.04	>84		
Dogs	0.0625	16±11.5	4.0±0.3	6.5±1.1	80±5.1	4.3±0.9	14±1.5		
($n = 4$)	0.125	97±2.0	4.9±0.8	22±2.8	99±0.3	3.4±0.9	34±2.4		
	0.25	100	2.3±0.3	43±5.5	100	1.0±0.2	56±5.0	0.080**	0.050**
	0.5	100	1.8±0.3	60±4.0	100	1.1±0.2	70±3.6	±0.007	±0.002
	1.0	100	1.8±0.2	80±5.7	100	1.1±0.2	93±8.3	$P<0.05$	
	2.0	100	1.4±0.4	88±11.4	100	1.1±0.3	>100		
	4.0	100	1.1±0.2	>41	100	0.9±0.2	>42		
Rhesus monkeys	0.0625	11†	5.5†	23†	20±9.0	2.1±0.2	8±4.2		
($n = 7$)	0.125	51±3.5	4.6±0.3	17±3.0	90±1.8	3.7±0.3	25±2.0		
	0.25	99±0.6	4.0±0.5	32±2.9	100	1.8±0.4	39±1.8	0.124	0.083
	0.5	100	1.0±0.04	53±5.7	100	0.6±0.07	56±4.0	±0.002	±0.008
	1.0	100	0.7±0.09	80±8.0	100	0.4±0.05	79±6.7	$P<0.01$	
	2.0	100	0.5±0.04	>96	100	0.4±0.12	>96		
	4.0	100	0.5±0.2	>68	100	0.3±0.08	>68		

neuromuscular block than the single twitch and that atracurium was significantly more potent in dogs than in either cats or rhesus monkeys. The time-course of neuromuscular blockade is also indicated in table I. The onset of maximum block was shorter with the greater doses whereas the time taken to reach full recovery was more prolonged. The time-course of the single twitch and tetanic contraction was not significantly different when doses which produced the same degree of block of these responses were compared.

In each species studied blockade of the single and tetanic responses of the gastrocnemius by atracurium was readily antagonized by neostigmine 0.05 mg kg^{-1} i.v. and by edrophonium 0.2 mg kg^{-1} i.v. Figure 3 shows a typical antagonism by neostigmine in an anaesthetized cat. Recovery from atracurium was compared with that from established competitive blocking agents using rate constants for recovery of the peak tetanic contraction in rhesus monkeys (table II). These rate constants show that recovery from neuromuscular blockade by atracurium was significantly faster than that from tubocurarine and dimethyl tubocurarine, but was comparable to recovery from pancuronium and fazadinium. Although the rate constants for gallamine and alcuronium were less than that for atracurium, the differences were not significant.

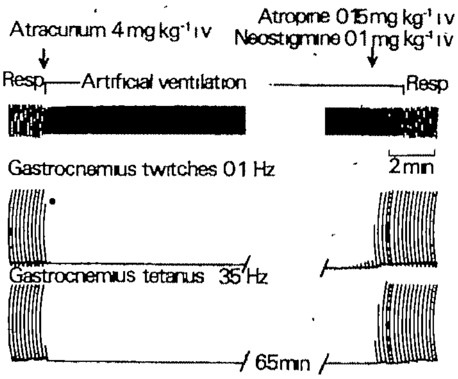

FIG. 3. Tracings from a cat anaesthetized with chloralose given atracurium 4 mg kg^{-1} i.v. Approximately 70 min later; neostigmine 0.1 mg kg^{-1} i.v., preceded by atropine 0.15 mg kg^{-1} i.v. rapidly antagonized blockade of the single twitch and tetanic responses (35 Hz) of the gastrocnemius muscles.

TABLE II. *Rate constants for recovery of the peak tetanic contraction of the gastrocnemius muscle using the first dose of each drug which caused complete neuromuscular block in groups of rhesus monkeys. Mean values are quoted with SEM. Asterisks denote rate constants significantly different from that of atracurium at the 5% (*) and 0.1% (***) levels respectively*

Drug	Dose i.v. (mg kg^{-1})	Rate constant (% per min)
Atracurium ($n = 7$)	0.25	9.2 ± 0.5
Tubocurarine ($n = 4$)	0 25	4.4 ± 0.6***
Dimethyl tubocurarine ($n = 4$)	0.04–0.12	6 6 ± 0.8*
Gallamine ($n = 4$)	0.5–2.0	7.8 ± 0.8
Alcuronium ($n = 4$)	0.08–0.16	6.8 ± 1.7
Pancuronium ($n = 4$)	0.01–0 02	10.6 ± 0.3
Fazadinium ($n = 4$)	0.5	8.2 ± 1.4

Interaction with halothane

In dose–response curves obtained from four anaesthetized cats, the doses of atracurium estimated to produce 50% neuromuscular paralysis were 0.110 ± 0.007 mg kg^{-1} i.v. in the presence of 1% halothane and 0.142 ± 0.016 mg kg^{-1} i.v. in controls, without halothane. The value for 2% halothane was 0.130 ± 0.032 mg kg^{-1} i.v.; control 0.183 ± 0.035 mg kg^{-1} i.v. These results for both 1 and 2% halothane were not significantly different from the respective controls. Although the mean time taken for recovery after complete blocking doses of atracurium 0.25–0.5 mg kg^{-1} i.v. was increased from 22 ± 2.6 min to 32 ± 3.3 min with 1% halothane and from 24 ± 3.6 min to 51 ± 18.5 min with 2% halothane, differences from the controls did not achieve significance.

Cholinesterase inhibition

The IC_{50} (μmol litre^{-1}) values for inhibition of human cholinesterase with acetylthiocholine as substrate, for neostigmine, atracurium and known neuromuscular blocking agents were: neostigmine, <1; fazadinium, 2; pancuronium, 14; alcuronium, 55; atracurium, 56; tubocurarine, 140; gallamine, 900; dimethyl tubocurarine, 1000.

The inhibitory activity of atracurium was less than that of neostigmine, fazadinium and pancuronium, but greater than that of tubocurarine, gallamine and dimethyl tubocurarine.

Autonomic and cardiovascular effects

Recordings from an anaesthetized cat (fig. 2) show that the bradycardia induced by vagal nerve stimulation, and the contraction of the nictitating membrane in response to sympathetic stimulation, were unimpaired after a dose of atracurium 0.25 mg kg^{-1} i.v. Dose–response curves for atracurium obtained from the results in anaesthetized cats, dogs and rhesus monkeys demonstrate that there is a wide separation between the doses required for neuromuscular paralysis and those that inhibit autonomic mechanisms. For example, figure 4 shows that atracurium caused appreciable vagal blockade only at doses 16 times the full neuromuscular paralysing dose in seven anaesthetized rhesus monkeys and that impairment of sympathetic function was minimal. Results in six anaesthetized cats and four anaesthetized dogs were similar.

In table III the doses required to produce 50% vagal block and 50% neuromuscular block have been estimated from the dose–response curves obtained from six anaesthetized cats and the ratios of these doses have been calculated. Results for known competitive neuromuscular blocking agents, quoted for comparison, have been reported previously (Hughes and Chapple, 1976a, b). There was a wide separation between the vagal and neuromuscular blocking doses for atracurium and dimethyl tubocurarine. For pancuronium and alcuronium, the separation between these doses was significantly less than that for atracurium and the separation had virtually disappeared for tubocurarine. In contrast, vagal blockade with gallamine and fazadinium occurred with doses less than those required for neuromuscular paralysis.

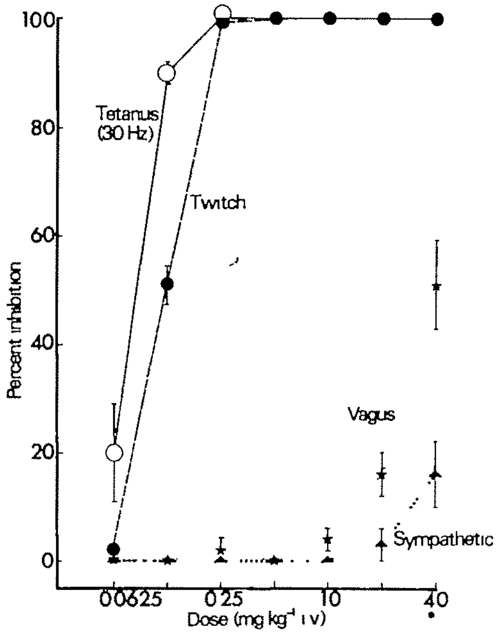

FIG. 4. Dose–response curves showing blockade of neuromuscular and autonomic mechanisms by atracurium given to seven anaesthetized rhesus monkeys (each point represents the mean of seven observations). ○——○ = Percentage inhibition of the tetanic responses of the gastrocnemius muscle to indirect stimulation at 30 Hz for 1 s every 10 s; ●——● = percentage inhibition of the twitch responses of the gastrocnemius muscle to induce stimulation at 0.1 Hz; ★- - -★ = percentage inhibition of the bradycardia responses to vagal stimulation at 10–20 Hz for 10 s; ▲ ··▲ = percentage inhibition of the vasopressor responses to carotid occlusion for 10 s. Vertical lines indicate SEM.

The lack of cardiovascular effect is illustrated in figure 2, which shows a tracing from an anaesthetized cat given atracurium 0.25 mg kg^{-1} i.v. The small transient changes in arterial pressure and heart rate were probably an artefact associated with the bolus injection and the commencement of artificial ventilation. The wide separation between the neuromuscular and cardiovascular effects of atracurium in six anaesthetized cats is shown in figure 5. Small insignificant increases in mean arterial pressure occurred after doses of

TABLE III. *Dose ratios for 50% vagal block (ED_{50}) and 50% neuromuscular (NM) block (ED_{50}) by atracurium in comparison with those for known competitive blocking agents in groups of anaesthetized cats. Mean values are quoted with SEM. Asterisks denote ratios significantly different from that of atracurium at the 5% level (*)*

Neuromuscular blocking agent	n	Vagal block ED_{50} (mg kg^{-1} i.v.)	NM block ED_{50} (mg kg^{-1} i.v.)	$\frac{\text{vagal } ED_{50}}{\text{NM } ED_{50}}$
Atracurium	6	3.08 ± 0.76	0.13 ± 0.01	24.4 ± 6.13
Dimethyl tubocurarine	4	0.50 ± 0.07	0.02 ± 0.003	24.6 ± 4.46
Pancuronium	4	0.08 ± 0.01	0.02 ± 0.002	5.2 ± 0.80*
Alcuronium	4	0.25 ± 0.05	0.05 ± 0.007	5.1 ± 1.31*
Tubocurarine	4	0.19 ± 0.01	0.13 ± 0.01	1.5 ± 0.15*
Gallamine	4	0.56 ± 0.07	0.83 ± 0.13	0.7 ± 0.12*
Fazadinium	4	0.29 ± 0.09	0.69 ± 0.15	0.5 ± 0.11*

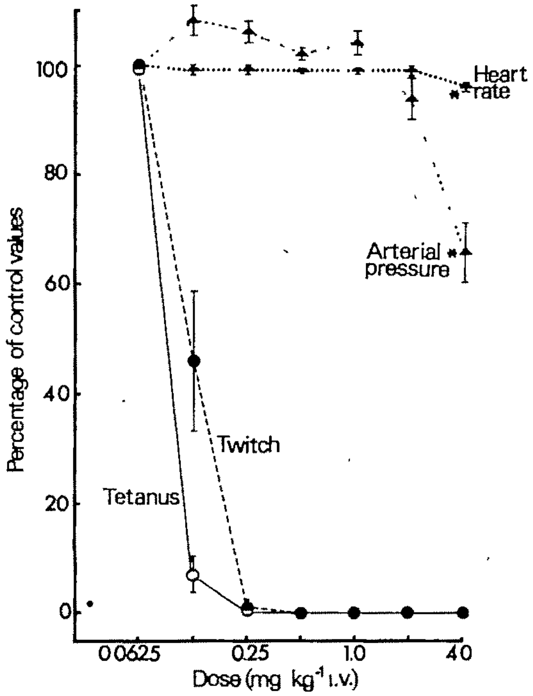

FIG. 5. Neuromuscular and cardiovascular effects of atracurium in six anaesthetized cats measured at time of maximum effect (each point represents the mean of six observations) Percentage of control values of. ○——○ = tetanic responses of the gastrocnemius muscle to indirect stimulation at 30 Hz for 1 s every 10 s; ●- - -● = twitch responses of the gastrocnemius muscle to indirect stimulation at 0.1 Hz; ▲- · -▲ = mean arterial pressure; ▲· · ▲ = heart rate. Vertical lines indicate SEM. Asterisks denote values for heart rate and arterial pressure significantly different from controls at the 1% level (*).

0.125–1 mg kg^{-1}; heart rate was unchanged. Significant hypotension and slight bradycardia were evident after 4 mg kg^{-1} i.v., but this dose was 16 times that required for full neuromuscular paralysis. Similar results were obtained in seven anaesthetized rhesus monkeys. In four anaesthetized dogs, atracurium 2 mg kg^{-1} i.v. reduced mean arterial pressure to 53 ± 20.2% of the control value, but this dose was eight times that required for full neuromuscular paralysis.

Experiments were carried out on four anaesthetized beagle dogs, allowed to recover fully after receiving excessive doses of atracurium. Each of two dogs received 2.5 mg kg^{-1} i.v., 10 times the dose required for full neuromuscular paralysis. Apnoea developed rapidly and artificial ventilation was required for 76 and 79 min respectively. Heart rate was reduced by 14 and 23% of control and the P and T waves of the electrocardiogram were reduced. The pupils were still responsive to light and no salivation was observed. Both dogs made an uneventful recovery after termination of anaesthesia. Each of the other two dogs, with an implanted aortic catheter for recording arterial pressure, received doses of atracurium 0.25, 0.5, 1.0 and 2.0 mg kg^{-1} i.v. (3.75 mg kg^{-1} total). These doses caused apnoea and artificial ventilation of the lungs was required for a mean 23, 48, 66 and 87 min respectively. The corresponding period indicates the time required for recovery after each dose. Cardiovascular effects were minimal after 0.25 and 0.5 mg kg^{-1} i.v., but the following changes occurred after doses of 1 and 2 mg kg^{-1} i.v. (i.e. four and eight times the full neuromuscular paralysing dose); in one dog mean aortic pressure was markedly reduced by 45 and 68% of control respectively and heart rate was slightly reduced by 15 and 7%. The QRS complex of the electrocardiogram was reduced and the T wave enlarged. After the same doses in the other dog, mean aortic pressure was reduced by 15 and 10% respectively and heart rate was increased by 20 and 21% of control. The P wave of the electrocardiogram was enlarged. In both dogs salivation occurred. Although breathing was fully restored after the last dose of atracurium, neostigmine 0.5 mg i.v. preceded by atropine 0.3 or 0.6 mg i.v., was given to ensure adequate reversal of the neuromuscular blockade. Both dogs made an uneventful recovery after termination of anaesthesia.

Haemodynamic studies

In each of five anaesthetized dogs i.v. doses of atracurium 0.0625 and 0.125 mg kg^{-1} had no important effects on the circulatory variables shown in table IV, including central venous pressure (not tabulated).

Doses of 0.25, 0.5 and 1.0 mg kg^{-1} i.v. slightly reduced phasic aortic flow, mean aortic pressure, heart rate, cardiac output and peripheral resistance. Maximum acceleration was reduced only by 1.0 mg kg^{-1} i.v. Central venous pressure was virtually unchanged; the T wave of the electrocardiogram was slightly enlarged. These small circulatory effects persisted for 5–60 min.

A dose of 2.0 mg kg^{-1} i.v. (eight times the full neuromuscular paralysing dose) reduced phasic aortic flow, mean aortic pressure, heart rate, cardiac output, maximum acceleration and peripheral resistance. Central venous pressure was

TABLE IV. *Effects of atracurium on phasic aortic flow, mean aortic pressure, heart rate, cardiac output, maximum acceleration and peripheral resistance in five anaesthetized open-chest dogs. Values at the time of maximum effect are expressed as mean percentages of initial measurements (= 100) with SEM. *Results in four dogs*

Dose (mg kg^{-1} i.v.)	Dose interval (min)	Phasic aortic flow: Initial (litre min^{-1})	Phasic aortic flow: Effect (initial = 100)	Mean aortic pressure (initial = 100)	Heart rate (initial = 100)	Cardiac output (initial = 100)	Maximum acceleration (initial = 100)	Peripheral resistance (initial = 100)
0.0625	20	9.44±0.65	106±4.1	100±1.6	97±1.1	98±5.5	104±4.1	102±2.2
0.125	40	10.54±0.51	105±2.4	102±1.3	97±1.8	107±4.5	104±2.0	101±3.7
0.25	60	10.04±0.73	99±3.8	94±3.2	97±1.6	89±3.4	98±2.7	100±3.8
0.5	75	8.56±0.69	96±6.0	88±1.5	90±1.0	86±6.1	106±7.6	96±8.6
1.0	90	7.12±0.34	93±2.4	81±4.8	90±1.2	96±7.1	90±6.3	85±4.8
2.0	90	7.04±0.53	77±6.4	61±9.6	83±1.9	74±8.3	71±5.4	80±9.6
4.0*		7.2±0.49	61±6.5	45±10.1	77±2.3	69±5.4	48±8.7	61±11.8

slightly increased; the T wave of the electrocardiogram was enlarged. One dog died after 28 min and a postmortem revealed atrophy of the right ventricle. In the four surviving dogs the circulatory effects persisted for about 90 min except for mean aortic pressure which, in two of the four dogs, was still reduced after this period. The four dogs received a further dose of 4.0 mg kg^{-1} i.v. which further reduced the circulatory variables; the T wave of the electrocardiogram was enlarged. All these dogs survived and were recovering for 45 min when the experiments were terminated.

In other experiments atracurium, at bath concentrations of 100 µg ml^{-1}, had no inotropic or chronotropic effects on spontaneously beating guineapig atria. This concentration is greatly in excess of the blood concentrations of atracurium likely to be encountered after full neuromuscular paralysing doses.

Histamine release

Evidence of histamine release was obtained only after administration of relatively large doses of atracurium to anaesthetized dogs which are known to release histamine readily. Doses of 10 mg kg^{-1} i.v. mepyramine and 15 mg kg^{-1} i.v. burimamide or cimetidine were sufficient to abolish the decrease in mean arterial pressure induced by histamine 20 or 40 µg kg^{-1} i.v. in each of four dogs (fig. 6). Such doses of the H_1- and H_2-receptor antagonists reduced, in part, the moderate hypotension caused by atracurium 2 mg kg^{-1} i.v. and greatly reduced the marked hypotension produced by tubocurarine 0.4 mg kg^{-1} i.v. It should be noted that the dose of atracurium used was eight times the neuromuscular paralysing dose while that of tubocurarine was, in fact, the paralysing dose in dogs.

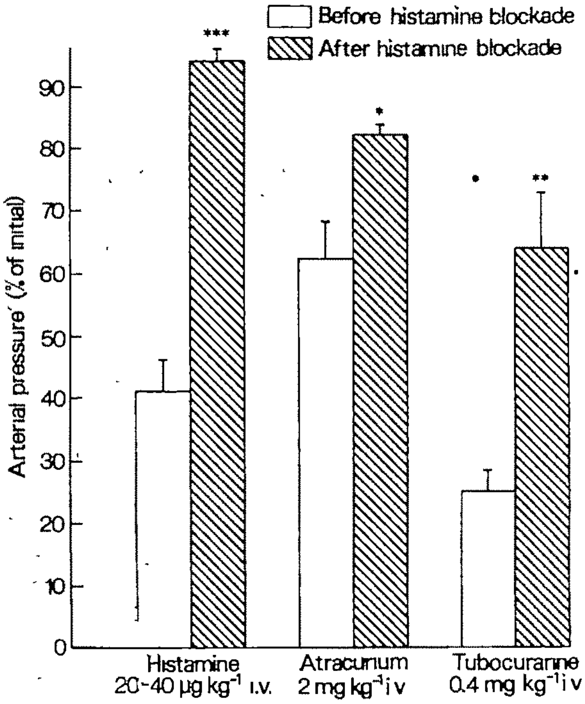

FIG. 6. Effects of atracurium, tubocurarine and histamine on arterial pressure before and after blockade of histamine receptors in four anaesthetized dogs. Mean values are shown and vertical lines indicate SEM. Asterisks denote significant differences after histamine blockade for each drug at the 5% (*), 2% (**) and 0.1% (***) levels respectively. (Full neuromuscular paralysing doses: atracurium 0.25 mg kg^{-1}; tubocurarine 0.4 mg kg^{-1}.)

Changes in acid–base balance

During respiratory acidosis, induced by ventilation with 20% carbon dioxide, neuromuscular paralysis of both responses was greater than in the control tests carried out before and after the acidosis, but the increase did not achieve statistical significance (table V). However, recovery of both the single twitch and tetanic responses was significantly longer during acidosis. Metabolic acidosis, caused by infusion of 8.4–12.0 mmol of hydrochloric acid 0.75 mol litre^{-1}, significantly enhanced blockade of the single twitch and also significantly prolonged recovery of the single twitch and tetanic responses as indicated in table V.

Paralysis of both neuromuscular responses was significantly reduced and recovery significantly shortened during respiratory alkalosis produced by increasing the tidal volume four-fold. Similarly, metabolic alkalosis, caused by infusion of 19.6–27.3 mmol of sodium bicarbonate 1 mol litre^{-1}, significantly reduced paralysis of the single twitch and significantly shortened recovery of the tetanic response as shown in table V.

In these experiments effects on paralysis of the tetanically stimulated muscles were obscured by the presence of complete blockade, but changes in recovery times followed those of the contralateral muscles stimulated by single shocks.

Elimination

The role of the liver was studied in four anaesthetized cats. From dose–response curves, the doses of atracurium estimated to produce 50% neuromuscular paralysis were 0.119 ± 0.013 mg kg^{-1} *via* the jugular vein and 0.121 ± 0.016 mg kg^{-1} *via* the hepatic portal vein; these values were not significantly different. Furthermore, the mean time taken for full recovery after a complete blocking dose of 0.25 mg kg^{-1} was similar when atracurium was given through the hepatic portal vein (27.1 ± 4.3 min) to that when given through the jugular vein (26.5 ± 5.8 min).

The involvement of the kidneys was also studied in four anaesthetized cats. From dose–response curves, the dose of atracurium estimated to produce 50% neuromuscular paralysis, was not significantly changed after renal ligation, whereas that for gallamine was significantly reduced (fig. 7). Although the mean time taken for recovery after complete blocking doses of atracurium 0.25–0.5 mg kg^{-1} i.v. was increased from 29 ± 2.9 min to 43 ± 9.2 min after renal ligation, the difference did not achieve significance. However, after complete blocking doses of gallamine 0.5–2.0 mg kg^{-1} i.v., renal ligation significantly prolonged recovery from 24 ± 3.7 min to 79 ± 14.3 min ($P < 0.05$).

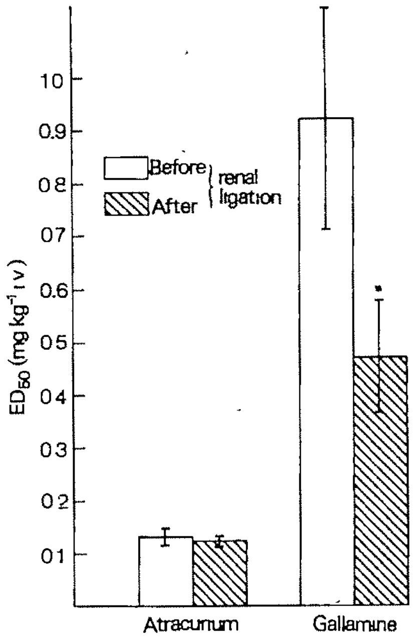

FIG. 7. Doses of atracurium and gallamine required to produce 50% neuromuscular paralysis (ED$_{50}$ mg kg^{-1} i.v.) before and after bilateral renal ligation in four anaesthetized cats for each drug. Mean values are shown and vertical lines indicate SEM. Asterisk denotes result for gallamine significantly different from control at the 5% level (*).

DISCUSSION

In a previous study with dimethyl tubocurarine, we concluded that this drug has desirable pharmacological properties, but there remains a need for a neuromuscular blocking agent with a similar highly specific action at the neuromuscular junction but of shorter duration (Hughes and Chapple, 1976b). It seems from our pharmacological assessment, that atracurium may possess these desirable properties.

The neuromuscular experiments demonstrated that atracurium is a potent competitive neuromuscular blocking agent. Paralysis was readily antagonized by anticholinesterases and, similar to other competitive agents, blockade was enhanced by halothane. The tetanic response was significantly more sensitive to paralysis than the single twitch, but the time taken for recovery from equal block of both responses was similar. It has also been demonstrated, in anaesthetized man, that the tetanic response is a more sensitive index than the single twitch for the assessment of neuromuscular blockade (Hughes, Ingram and Payne, 1976).

TABLE V. *Effects in anaesthetized cats of respiratory and metabolic acidosis and alkalosis on pH, P_{CO_2}, P_{O_2}, arterial pressure and neuromuscular paralysis by atracurium. pH, P_{CO_2} and P_{O_2} measurements shown were made at maximum effect of each dose. Paralysis was determined in both gastrocnemius muscles stimulated indirectly, one with single shocks at 0.1 Hz and the other tetanically at 30 Hz every 10 s. Mean values (with ranges) for groups of cats (n = number of cats) are shown before (pre-control), during, and after (post-control) the treatment period. Asterisks denote differences between control and treatment values significant at the 5% (*), 1% (**) and 0.1% (***) levels respectively*

								Single shock stimulation		Tetanic stimulation	
Treatment	*n*	Atracurium standard dose i.v (mg kg^{-1})	Procedure	pH (units)	P_{CO_2} (mm Hg)	P_{O_2} (mm Hg)	Arterial pressure (mm Hg)	Paralysis (%)	Recovery time (min)	Paralysis (%)	Recovery time (min)
Respiratory acidosis, inhalation of 20% carbon dioxide	5	0 16 (0 125–0 24)	Pre-control	7 33*** (7 26–7.36)	35** (30–41)	281 (117–453)	117 (94–142)	25 (0–66)	8* (0–14)	90 (75–99)	20* (13–30)
			Acidosis	6 85 (6 62–7.00)	118 (79–146)	293 (117–403)	111 (60–147)	63 (30–99)	14 (10–23)	97 (95–100)	28 (19–38)
			Post-control	7 36*** (7 26–7 48)	39** (30–51)	277 (122–420)	80 (48–110)	36 (0–93)	7* (0–12)	94 (88–99)	21* (15–31)
Metabolic acidosis, infusion of 9 8 mmol of HCl 0.75 mol litre^{-1} (8 4–12)	4	0 15 (0 125–0 175)	Pre-control	7 35** (7 29–7.39)	37 (28–50)	172* (103–244)	137* (115–155)	29* (4–61)	9* (5–13)	98 (96–99)	20 (15–25)
			Acidosis	6 82 (6 69–6 93)	36 (27–42)	258 (157–360)	108 (83–135)	70 (35–88)	15 (9–21)	100 (99–100)	29 (23–35)
			Post-control	7 32*** (7.28–7.37)	37 (28–44)	245 (188–301)	106 (96–119)	44* (16–73)	14 (7–21)	96 (86–100)	20** (16–26)
Respiratory alkalosis, Hyperventilation, four-fold	8	0 15 (0 125–0 2)	Pre-control	7 31*** (7 26–7 35)	44*** (35–51)	259 (66–452)	121*** (103–144)	38** (15–67)	9* (7–13)	94 (80–100)	19 (12–26)
			Alkalosis	7 63 (7 56–7 73)	16 (13–21)	230 (63–482)	82 (61–107)	18 (0–41)	6 (0–10)	85 (53 – 100)	18 (9–41)
			Post-control	7 28*** (7 21–7 35)	41*** (32–51)	208 (68–429)	111*** (83–133)	51** (9–92)	11* (7–21)	94* (68–100)	22* (11–37)
Metabolic alkalosis, Infusion of 24 1 mmol of Na_2CO_3 1 mol litre^{-1} (19 6–27 3)	4	0 14 (0 125–0 15)	Pre-control	7 29** (7 23–7 33)	40 (36–43)	295 (276–309)	116 (95–140)	45* (26–59)	8 (5–12)	98 (95–100)	21** (17–27)
			Alkalosis	7 66 (7 55–7 74)	40 (35–44)	297 (273–315)	108 (103–113)	21 (5–41)	8 (3–13)	91 (84–100)	13 (10–17)
			Post-control	7 32** (7 27–7 35)	51 (43–63)	267* (227–293)	109 (103–116)	55* (22–95)	10 (7–13)	100 (99–100)	19* (15–22)

Although atracurium was significantly more potent in dogs than in either cats or rhesus monkeys, the time-course of neuromuscular blockade was similar throughout these species. This observation may be important, since it has been reported that the duration of action of some competitive blocking agents was longer in monkeys, as in man, than in other species (Biggs, Davis and Wien, 1964; Mushin and Mapleson, 1964; Bamford et al., 1967; Busfield et al., 1968; Hughes, 1972; Hughes and Chapple, 1976b; Hughes, Payne and Sugai, 1976). In comparison with established drugs, it was shown that atracurium was intermediate in its course of action. For example, in anaesthetized monkeys, recovery from neuromuscular blockade by atracurium was significantly faster than recovery from tubocurarine and dimethyl tubocurarine, but was comparable to that of other available competitive drugs with a medium duration of action.

Cholinesterase inhibition by atracurium is unlikely to be of importance since IC_{50} for the human enzyme corresponds to a concentration of approximately 70 μg ml^{-1}. This concentration is greatly in excess of that likely to occur after neuromuscular paralysing doses of atracurium.

An important feature of atracurium was the wide separation between doses required for neuromuscular paralysis and those which inhibit autonomic mechanisms. It is well established that vagal blockade in man causes undesirable tachycardia and hypertension. In this respect, the vagolytic effect of atracurium, like that of dimethyl tubocurarine, was substantially less than that of other competitive agents currently used in anaesthetic practice. Unlike tubocurarine, the impairment of sympathetic function was minimal even at supramaximal neuromuscular paralysing doses. However, some consider that inhibition of catecholamine uptake may contribute in part to the cardiovascular effects associated with administration of pancuronium (Ivankovich et al., 1975; Docherty and McGrath, 1977). Dr L. G. Garland of our laboratories has carried out a preliminary study of catecholamine uptake using perfused rat hearts similar to that described by Iversen (1963) and used recently by Salt, Barnes and Conway (1980) for experiments with pancuronium analogues. It was found that atracurium partially blocked both uptake processes, but only at concentrations in excess of those likely to occur after neuromuscular paralysing doses. $Uptake_2$ was inhibited more strongly than $Uptake_1$; the corresponding IC_{50} values were 20 μg ml^{-1} and 100 μg ml^{-1} respectively. No doubt the absence of effect on the various autonomic mechanisms has contributed to the cardiovascular stability associated with atracurium. Significant hypotension and slight bradycardia occurred only with doses 16 times that required for full neuromuscular paralysis in anaesthetized cats and rhesus monkeys and in dogs circulatory depression only became of importance at eight times this dose. *In vitro* atrial preparations indicated the absence of direct inotropic and chronotropic effects. Indirect evidence obtained from anaesthetized dogs suggests that the cardiovascular effects of atracurium were attributable mainly to histamine release; unlike tubocurarine, such effects occurred only after doses of atracurium eight times the full neuromuscular paralysing dose. However, since the hypotensive action of atracurium was not completely blocked by H_1- and H_2-receptor antagonists, sympathetic blockade may also play a minor role. The margin of safety with atracurium was also exemplified in those experiments in which very large doses of atracurium were given to anaesthetized dogs which made an uneventful recovery from the neuromuscular blockade and anaesthesia.

In vitro studies, carried out by colleagues in our Central Analytical Laboratories, Dartford, have shown that when atracurium is incubated at 37 °C in buffers of appropriate pH, its non-enzymic decomposition was at least three times faster when the pH was increased from 6.9 to pH 7.6. Analysis of the decomposition products by high performance liquid chromatography verified that this route of inactivation was by "Hofmann Elimination". We may have demonstrated the "Hofmann" mechanism *in vivo* in anaesthetized cats, since neuromuscular paralysis by atracurium was significantly reduced when the arterial pH was increased by respiratory and metabolic alkalosis; conversely, paralysis was significantly enhanced when the arterial pH was reduced by respiratory and metabolic acidosis.

Experiments in anaesthetized cats indicate that atracurium was not rapidly taken up by the liver, unlike a previous neuromuscular blocker, BW403C65, with which there was a three-fold reduction in its paralysing potency when the compound was given through the hepatic portal vein (Hughes, 1972). Furthermore, the results after renal ligation indicated that, unlike gallamine, the kidneys are not a major route for the elimination of unchanged atracurium.

We conclude from this study that the pharmacological properties of atracurium are of sufficient interest to merit its evaluation as a neuromuscular blocking agent in anaesthetized man.

ACKNOWLEDGEMENTS

We are grateful to Dr J. B. Tateson and Miss M. Webb for carrying out the cholinesterase inhibition experiments and to Mr M. D. Shelley and Mrs J. S. Clark for skilled technical assistance.

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PHARMACOLOGIE DE L'ATRACURIUM: NOUVEL AGENT DE BLOCAGE NEUROMUSCULAIRE CONCURRENT

RESUME

L'Atracurium besylate, 2,2'-(3,11-dioxo-4,10-dioxatridecylène)-bis-[6,7-diméthoxy-1-(3,4-diméthoxybenzyl)-2-méthyl-1,2,3,4,-tétrahydroisoquinolinium] dibenzènesulphonate, appartient à une nouvelle série d'agents de blocage neuromusculaire concurrent. Une dose intraveineuse de 0,25 mg kg^{-1}, produit une paralysie complète chez les chats, chiens et singes rhésus anesthésiés; la paralysie a été de durée moyenne et a été immédiatement neutralisée par la néostigmine. Le blocage pneumogastrique ne s'est produit qu'après des doses de 8 à 16 fois supérieures à la dose produisant la paralysie neuromusculaire complète et les effets sur les mécanismes sympathiques ont été minimaux. L'hypotension et la bradycardie se sont manifestées après des doses supramaximales de 4 mg kg^{-1} administrées par voie intraveineuse, et ces effets, de même que la dépression circulatoire, sont probablement attribuables au dégagement d'histamine. Les études que l'on a faites *in vitro* ont montré que la décomposition non enzymatique de l'atracurium par "Élimination d'Hoffmann" est activée par l'augmentation du pH. *In vivo*, la paralysie neuromusculaire a été réduite d'une manière significative lorsque le pH artériel a été augmenté. Il n'y a aucune indication permettant de dire que le foie ou les reins jouent un rôle important dans le métabolisme et dans l'élimination du médicament inchangé. Ces résultats présentent un intérêt suffisant pour mériter que l'on procède à l'évaluation de l'atracurium sur l'homme anesthésié.

DIE PHARMAKOLOGIE VON ATRACURIUM. EIN NEUES, KONKURRENZFAHIGES NEUROMUSKULÄRES BLOCKIERUNGSMITTEL

ZUSAMMENFASSUNG

Atracuriumbesylat, 2,2'-(3,11-dioxo-4,10-dioxatridecylen)-bis-[6,7-dimethoxy-1-(3,4-dimethoxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinolinium] dibenzenesulphonat, ist eines aus einer neuen Serie konkurrenzfähiger neuromuskulärer Blockierungsmittel. Eine intravenose Dosis von 0,25 mg kg^{-1} bewirkte völlige Lähmung bei narkotisierten Katzen, Hunden und Rhesusaffen; die Lähmung war von

mittlerer Dauer und konnte schnell von Neostigmin aufgehoben werden. Vagus-Blockierung trat erst nach Dosen auf, die 8–16 mal grösser waren als die volle Dosis fur neuromuskulare Lähmung, und die Auswirkungen auf sympathische Mechanismen waren minimal. Hypotension und Bradykardie zeigten sich nach übermaximalen intravenosen Dosen von 4 mg kg^{-1}, was zusammen mit Kreislaufdampfungen wahrscheinlich auf Histaminfreigabe zuruckzufuhren war. Studien *in vitro* zeigten, dass der nichtenzymische Abbau von Atracurium durch "Hoffmannsche Ausscheidung" durch eine Erhohung von pH gefördert wurde. *In vivo* wurde neuromuskuläre Lähmung wesentlich reduziert, wenn arterielles pH erhöht wurde. Es gab Anzeichen dafür, dass weder Leber noch Nieren eine wesentliche Rolle im Abbau und der Ausscheidung der unveranderten Droge spielen. Diese Ergebnisse sind interessant genug, um eine Beurteilung von Atracurium bei narkotisierten Menschen zu rechtfertigen.

LA FARMACOLOGIA DEL ATRACURIOM: UN NUEVO Y COMPETITIVO AGENTE DE BLOQUEO MUSCULAR

SUMARIO

El atracuriom besilate, con composición de 2,2-(3,11-dioxo-4,10-dioxatridecileno)-bis-[6, 7-dimetoxi-1-(3, 4-dimetoxibencilo)-2-metilo-1,2,3,4-tetrahidroisoquinoliniom] dibenceno de sulfuro, formá parte de una nueva serie de competitivos agentes de bloqueo neuromuscular. Una dosis intravenosa de 0,25 mg kg^{-1} produjo una parálisis total en gatos, perros y macacos de la India anestesiados; la parálisis fue de duración media y rápidamente contrarrestada por la neostigmina. El bloqueo vagal tuvo lugar tan sólo después de administrar dosis de 8 a 16 veces mayores que la correspondiente a la dosis de parálisis neuromuscular total y los efectos sobre los mecanismos simpáticos fueron mínimos. La hipotensión y la bradicadia fueron evidentes después de dosis supramáximas de 4 mg kg^{-1} de carácter intravenoso, y estos efectos, junto con la depresión circulatoria, pueden seguramente atribuirse a la aparición de histamina. Los estudios *in vitro* han demostrado que la descomposición no enzímica del atracuriom, mediante la "Eliminación Hofmann", fue intensificada por el pH creciente. La parálisis neuromuscular *in vivo* se redujo de forma significativa cuando el pH arterial se incrementó. Hubo indicaciones de que el hígado y el riñón no juegan un papel importante en el metabolismo ni en la eliminación de drogas inalteradas. Estos resultados son de suficiente interés como para merecer la evaluación del atracuriom en el hombre anestesiado.

Br. J. Anaesth. (1981), 53, 45

EVALUATION OF ATRACURIUM IN ANAESTHETIZED MAN

J. P. PAYNE AND R. HUGHES

SUMMARY

Atracurium is a potent competitive neuromuscular blocking agent in anaesthetized man with no cardiovascular effects at doses required for paralysis. Endotracheal intubation can be accomplished after i.v. doses of 0.6 and 0.3 mg kg^{-1}, within 1 and 2 min respectively. Paralysis is readily antagonized by neostigmine and is enhanced by halothane. The consistent response in terms of block and recovery which emerged when the drug was given as increments of 0.05 or 0.1 mg kg^{-1} indicates the absence of cumulative effects. The course of action of atracurium was appreciably shorter than that of other recognized competitive blocking agents. Doses of 0.3–0.6 mg kg^{-1} i.v. provided adequate relaxation during surgical intervention for 15–45 min; spontaneous recovery without the use of neostigmine was observed in some patients. In addition to the non-enzymic decomposition by "Hofmann Elimination", atracurium may also undergo an enzymic ester hydrolysis but, unlike suxamethonium, it may not be destroyed by pseudocholinesterase.

Studies in laboratory animals have shown that atracurium is a potent competitive neuromuscular blocking agent with a wide separation between the neuromuscular paralysing dose and that causing cardiovascular effects (Hughes and Chapple, 1980, 1981). On the basis of promising laboratory studies a quantitative evaluation of this drug has been carried out in anaesthetized man. Preliminary accounts of this work have already been reported (Hughes, Hunt and Payne, 1980; Hunt, Hughes and Payne, 1980; Hughes et al., 1980).

METHODS

Studies were performed in 62 patients, aged 21–78 yr (average 53 yr), who had given informed consent and who were about to undergo urological surgery at St Peter's Hospital, London. The trial was conducted with the authority of a Clinical Trial Certificate issued by the Committee on Safety of Medicines. Approval was also obtained from the Ethics Committee of St Peter's Hospital. For the purpose of the clinical trial atracurium was prepared as a 10-mg ml^{-1} solution in water for injection B.P. and was stored in 3-ml ampoules at 2–5 °C. The stability of the solution was tested at regular intervals by high performance liquid chromatography (HPLC). Atracurium was given in single and divided doses in the range of 0.05–0.6 mg kg^{-1} i.v.

No premedication was given and anaesthesia was induced with 5% thiopentone 400–600 mg given i.v. In a group of 42 patients intubation was achieved without the use of a neuromuscular blocking agent under anaesthesia with 2–4% halothane and after spraying the larynx with 4% lignocaine. In 33 of these patients the halothane was then withdrawn and anaesthesia was maintained with 60–66% nitrous oxide in oxygen using intermittent positive pressure ventilation of the lungs. Supplements of 50 or 100 mg of thiopentone and 0.05 or 0.1 mg of fentanyl were given i.v. as required. In the remaining nine patients ventilation was continued with 1% halothane in oxygen. In another group of 11 patients the practicality of endotracheal intubation after the administration of atracurium was investigated during anaesthesia with 60–66% nitrous oxide in oxygen.

The techniques used for the quantitative assessment of neuromuscular blockade have been described in detail elsewhere (Hughes, Ingram and Payne, 1976). Simultaneous recordings of the tetanic and single twitch contractions of the adductor pollicis muscles were obtained by stimulating each ulnar nerve supramaximally at the wrist every 12 s, one with tetanic bursts of 50 Hz for 1 s and the other with single shocks. The arterial

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pressure was measured directly from a polyethylene catheter inserted into the radial artery and, with the electrocardiogram, was recorded continuously throughout each study. The heart rate was measured from the electrocardiogram. In seven patients central venous pressure was recorded by inserting a catheter through the left brachial vein so that its tip lay in the region of the right atrium. Arterial blood-gas analyses were performed on samples taken from the radial artery before and 10–15 min after administration of the drug and were maintained within normal limits. Arterial or venous blood samples for haematological and biochemical examination were taken just before and 24 h after the patient had received atracurium.

In five patients rate and depth of ventilation was adjusted to produce states of respiratory acidosis and alkalosis to test the validity of the suggestion that the rate of inactivation of atracurium is influenced by changes in pH (Hughes and Chapple, 1980, 1981). Initially, the patients were under-ventilated for 20–40 min; thereafter a neuromuscular blocking dose of atracurium 0.2 mg kg^{-1} was given i.v. and the rate constant for the recovery of the sustained tetanus was determined. When recovery was complete the ventilation was suitably increased and after 15 min the same dose of atracurium was given and the whole procedure was repeated.

A separate group of nine patients was given atracurium during routine anaesthetic practice to assess the muscular relaxation during surgery.

Statistical analysis was by Student's *t*-test.

RESULTS

Stability. In each of the two clinical trials analysis by HPLC showed a total decomposition of 2.7 and 3.0% respectively during a period of 7 months.

Neuromuscular blockade. I.v. doses of atracurium 0.2 mg kg^{-1} caused complete neuromuscular block of the tetanic responses of the adductor pollicis muscle, whereas a dose of 0.3 mg kg^{-1} i.v. was required to produce full block of the single twitch in most patients (fig. 1, table I). The onset of maximum block of the tetanic response was shorter and its duration was longer than that of the single twitch. Once recovery had begun, the recovery phase of the tetanic response was slower than that of the single twitch. During recovery the tetanic response consists of two components, the peak tetanic contraction and the sustained tetanus

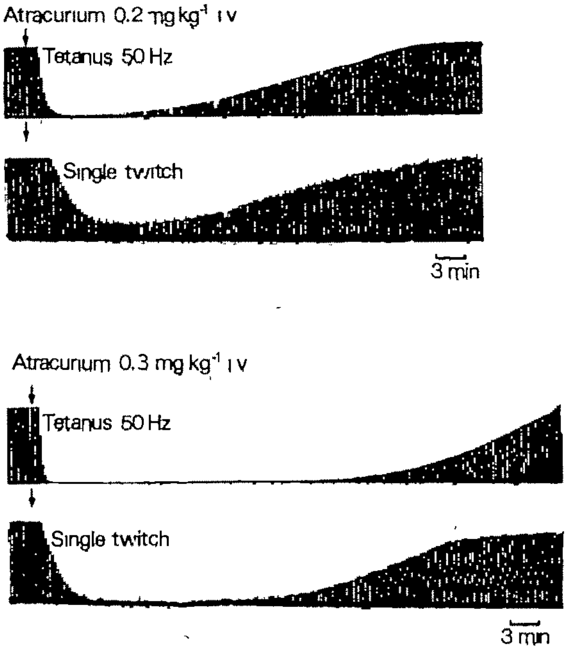

FIG. 1. Tracings from two anaesthetized patients showing neuromuscular paralysis of the tetanic and single twitch responses of the adductor pollicis muscle by 0.2- and 0.3-mg kg^{-1} i.v. doses of atracurium.

TABLE I. *Neuromuscular and cardiovascular effects of atracurium. Mean results are quoted and are expressed as percentages of the control values (±SEM)*

Dose (mg kg^{-1})	Percentage of control values			
	Adductor pollicis		Arterial pressure	Heart rate
	Tetanus	Twitch		
0.2 ($n = 10$)	0.6±0.5	19±3.5	99±0.6	100±0.7
0.3 ($n = 9$)	0	2±1.1	99±0.6	99±1.2
0.6 ($n = 9$)	0	0	96±1.7	103±1.0

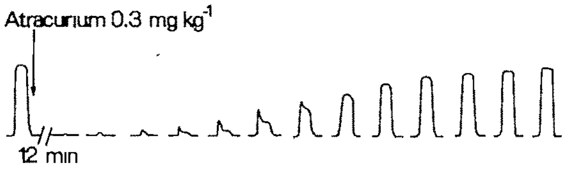

FIG. 2. Tetanic responses of the adductor pollicis muscle (50 Hz for 1 s every 12 s) shown at 3-min intervals during recovery from neuromuscular blockade by atracurium 0.3 mg kg^{-1} i.v.

TABLE II. *Time course of neuromuscular blockade of the tetanic responses of the adductor pollicis muscle by atracurium. Mean results are quoted with SEM. Asterisks denote values significantly different from the 0.2-mg kg*$^{-1}$ dose at the 5% (*) *and 0.1%* (***) *levels respectively*

Dose (mg kg^{-1})	Onset of maximum effect (min)	Duration of maximum effect (min)	95% recovery of peak contraction (min)	Rate constant for recovery of sustained tetanus (% per min)
0.2 ($n = 9$)	2.8±0.3	5.6±0.6	28.9±2.3	12.0±1.0
0.3 ($n = 7$)	1.9±0.1*	15.5±1.8***	34.9±1.9	10.1±0.6
0.6 ($n = 6$)	1.2±0.1***	33.7±3.0***	34.5±4.4	12.4±1.4

(fig. 2). At the beginning of recovery the peak tetanic contraction decreased rapidly to a plateau where the contraction was sustained until the end of the stimulus. As recovery proceeded the tetanic fade disappeared progressively until the tetanus was fully sustained.

A quantitative assessment of the time-course of blockade by atracurium of the tetanic responses of the adductor pollicis muscle is shown in table II. Statistical analysis showed that the onset of complete block was significantly shortened by increasing the dose from 0.2 to 0.3 mg kg^{-1} i.v. and from 0.3 to 0.6 mg kg^{-1} i.v. This same increase in dose also significantly prolonged the duration of maximum block at each dose. However, once recovery had begun there was no significant difference either in the time taken to achieve 95% recovery of the peak tetanic contraction, or in the rate constants for recovery of the sustained tetanus for these doses. (The rate constants were calculated by measuring the height of the sustained tetanus every 2 min until 95% recovery. Each measurement was subtracted from the pre-dose values and the difference transformed to its natural logarithm. Each logarithm was then plotted against time and the slope of the line calculated by regression analysis.)

The effectiveness of neostigmine as an antagonist was investigated under two conditions. The top tracing in figure 3 was taken from a patient who had received a total dose of 0.3 mg kg^{-1} of atracurium. When recovery of the tetanic response had reached 50%, neostigmine 2.5 mg, preceded by atropine 1.2 mg, produced a rapid antagonism of the neuromuscular block. Similar results were obtained in two other patients. The lower tracing

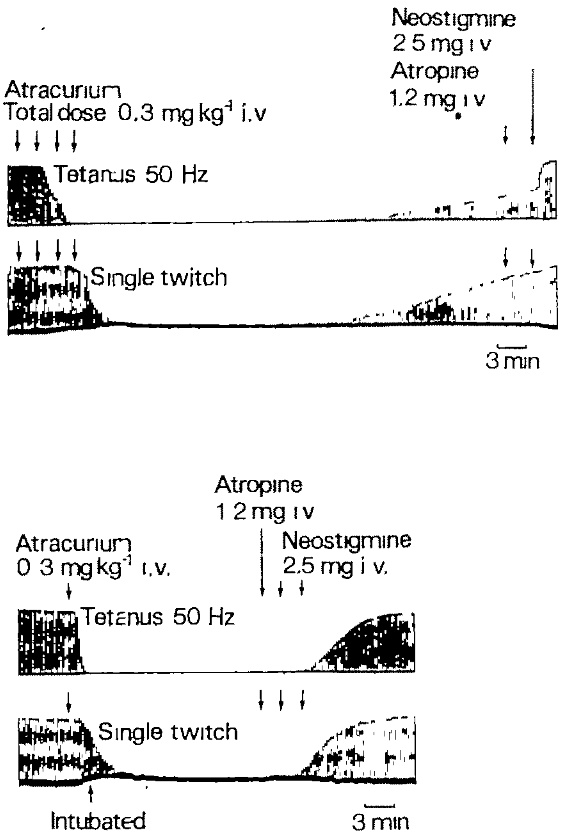

FIG 3. Recordings of the tetanic and single twitch responses of the adductor pollicis muscle from two anaesthetized patients who received atracurium 0.3 mg kg^{-1} i.v. in divided and single doses. Top tracings show rapid antagonism by neostigmine 2.5 mg given when recovery of tetanic response had reached 50%. Lower tracings show that intubation was accomplished within 2 min of administration of atracurium and, 20 min later, complete block was reversed by neostigmine 2 × 2.5 mg

in figure 3 shows the other situation. A single dose of atracurium 0.3 mg kg^{-1} produced complete block of the tetanic and twitch responses of the adductor pollicis muscles. Twenty minutes later, while complete block still persisted, neostigmine in two doses of 2.5 mg, preceded by atropine 1.2 mg, produced full recovery in a further 10 min. In two other patients who also received atracurium 0.3 mg kg^{-1}, two doses of neostigmine 2.5 mg given after 10 min induced complete antagonism in 15 and 18 min respectively. Figure 4 shows a similar study in a patient who had received atracurium 0.6 mg kg^{-1}. Two doses of neostigmine 2.5 mg given 20 min later produced a steady recovery from complete block of both the tetanic and single twitch responses of the adductor pollicis muscles. In two patients who had received the same dose of atracurium 0.6 mg kg^{-1}, neostigmine, when given after 10 and 15 min respectively, induced a similar antagonism of neuromuscular blockade.

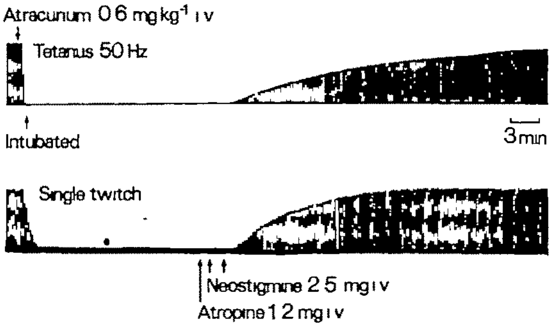

FIG. 4. Recording of the tetanic and single twitch responses of the adductor pollicis muscle from a patient given atracurium 0.6 mg kg^{-1} i.v. Intubation was achieved within 1 min and neostigmine 2 × 2.5 mg, given 20 min later, antagonized complete block.

Endotracheal intubation. In two patients, who were given atracurium 0.3 mg kg^{-1} after the recording arrangements had been completed and 30–45 min after inducing anaesthesia, intubation was accomplished in 1.5 and 2 min respectively. At that time the vocal cords were relaxed and blockade of the tetanic response of the adductor pollicis was complete (see fig. 3, lower trace). Three other patients received a dose of 0.6 mg kg^{-1}; the cords were relaxed within 1 min when intubation was achieved without difficulty (see fig. 4).

In three other patients atracurium was given immediately after induction of anaesthesia with thiopentone and so without neuromuscular and cardiovascular recordings except for the electrocardiogram. These patients received a dose of 0.3 mg kg^{-1} and the trachea was intubated after 1.0–1.75 min when breathing had ceased. Similarly, when three further patients were given 0.6 mg kg^{-1}, intubation was accomplished in 50–55 s.

Repeated dosage. Three patients were given an initial dose of atracurium 0.3 mg kg^{-1} followed by an incremental dose of 0.05 mg kg^{-1} when recovery of the single twitch had reached 50% of the initial response. The results in table III show a fairly consistent pattern in terms of the depth of blockade and the time taken to reach 50% recovery after three incremental doses of atracurium.

TABLE III. *Neuromuscular effects in each of three anaesthetized patients of repeated doses of atracurium 0.05 mg kg^{-1} i.v. given when recovery of the single twitch had reached 50%*

Neuromuscular block (%)			Time to 50% recovery of initial (min)		
Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3
73	62	60	5.5	5	4.5
83	81	79	9.5	8.5	10
68	68	68	5.5	6	6.5

Three other patients also received an initial dose of atracurium 0.3 mg kg^{-1}, but this dose was followed by an incremental dose of 0.1 mg kg^{-1} when recovery of the peak tetanic contraction had reached 50% of the initial response. A typical tracing is shown in figure 5 and the results of three such incremental doses are given in table IV. A consistent pattern emerged in terms of the depth of blockade and the time taken to reach 50% recovery.

Cardiovascular effects. Simultaneous recordings, taken at fast paper speed, of the electrocardiogram, arterial pressure, central venous pressure and the tetanic and single responses of the adductor pollicis muscles showed that a neuromuscular paralysing dose of 0.25 mg kg^{-1} had no effect on the electrocardiogram, arterial pressure or the central venous pressure. The absence of cardiovascular effects after doses of 0.2 and 0.3 mg kg^{-1} is indicated in table I. Even at

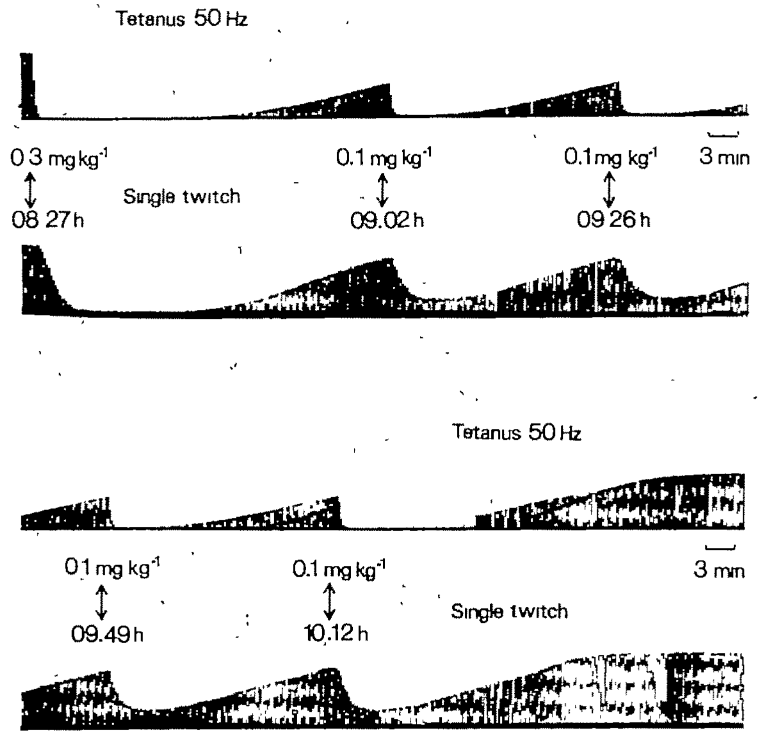

FIG. 5. Continuous recording of the tetanic and single twitch responses of the adductor pollicis from a patient who received an initial dose of atracurium 0.3 mg kg^{-1} i.v. Incremental doses of 0.1 mg kg^{-1} were given when recovery of the peak tetanic contraction had reached 50%. Arrows indicate dose (mg kg^{-1} i.v.) and time of administration.

TABLE IV. *Neuromuscular effects in each of three anaesthetized patients of repeated doses of atracurium 0.1 mg* kg^{-1} *i.v. given when recovery of the peak tetanic contraction had reached 50%*

Neuromuscular block (%)			Time to 50% recovery of initial (min)		
Dose 1	Dose 2	Dose 3	Dose 1	Dose 2	Dose 3
96	99	99	18	18	17
99	96	97	18	18	18
94	96	96	14	14	14

0.6 mg kg^{-1}, double the full paralysing dose, there were no significant changes in arterial pressure and heart rate.

Interaction with halothane. In a group of three patients given atracurium 0.2 mg kg^{-1} the mean block of the twitch response of the adductor pollicis muscle in the presence of 1% halothane was 91±4.2%. However, in a group of nine patients who did not receive halothane the mean block of 74±4.4% was less ($P = 0.05$). An assessment of the time-course of neuromuscular blockade by atracurium in the presence of 1% halothane is shown in table V. There was no significant difference in the onset of full block of the tetanic responses of the adductor pollicis muscles after doses of 0.2, 0.3 and 0.6 mg kg^{-1} in comparison with those patients who did not receive halothane as shown in table II; the duration of full block was only significantly longer with halothane after the 0.2-mg kg^{-1} dose. However, once recovery of the peak tetanic contraction had begun, it was significantly slower in the presence of halothane at each dose. In contrast, halothane had no effect on the single twitch response. Although the rate constants for recovery of the sustained tetanus were reduced with halothane, the differences were only significant after the 0.6-mg kg^{-1} dose.

Comparison with known drugs. Figure 6 shows the recovery of the peak tetanic contraction after

TABLE V. *Time-course of neuromuscular blockade of the tetanic responses of the adductor pollicis muscle by atracurium in the presence of 1% halothane. Mean results are quoted with SEM. Asterisks denote values significantly different from the controls (shown in table II) at the 5% (*) and 1% (**) levels respectively*

Dose (mg kg^{-1})	Onset of maximum effect (min)	Duration of maximum effect (min)	95% recovery of peak contraction (min)	Rate constant for recovery of sustained tetanus (% per min)
0.2 (n = 3)	2.0	12.3±2.6**	39.2±3.4*	9.0±0.4
0.3 (n = 3)	2.0	12.7±1.4	44.0±2.9*	7.4±1.5
0.6 (n=3)	1.1±0.2	31.7±1.1	51.0±1.9*	6.9±1.0*

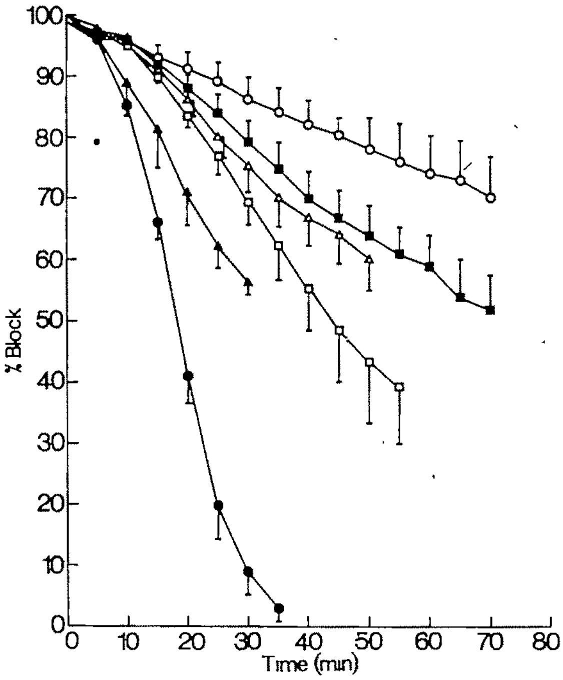

FIG. 6. Recovery of the peak tetanic contraction of the adductor pollicis muscle after neuromuscular paralysis by i.v. doses of: ○——○ dimethyl tubocurarine 0.1–0.3 mg kg^{-1} (n = 6); ■——■ tubocurarine 0.2–0.5 mg kg^{-1} (n = 6); △——△ pancuronium 0.05–0.06 mg kg^{-1} (n = 5); □——□ fazadinium 0.4–0.8 mg kg^{-1} (n = 6); ▲——▲ gallamine 1.0–1.5 mg kg^{-1} (n = 3); ●——● atracurium 0.2 mg kg^{-1} (n = 5). Each point represents the mean value in a number of patients (n) and vertical lines indicate SEM.

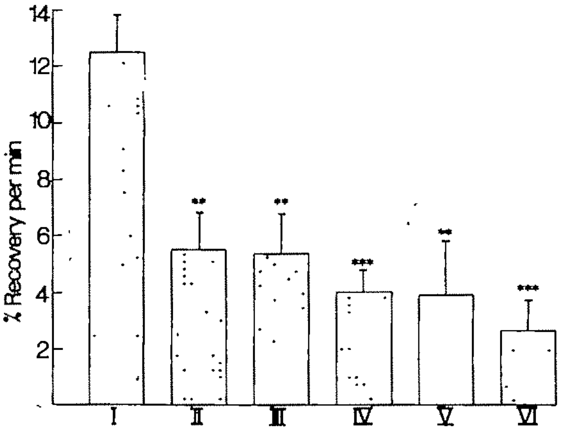

FIG. 7. Rate constants for recovery of the sustained tetanus of the adductor pollicis muscle from neuromuscular blockade by atracurium 0.2 mg kg^{-1} (I; n = 7), fazadinium 0.4–0.8 mg kg^{-1} (II; n = 5), tubocurarine 0.2 mg kg^{-1} (III; n = 6), gallamine 1.0–1.6 mg kg^{-1} (IV; n = 5), pancuronium 0.05–0.06 mg kg^{-1} (V, n = 5) and dimethyl tubocurarine 0.075–0.2 mg kg^{-1} (VI; n = 5).

neuromuscular blockade by atracurium and by five established agents. The data for the established drugs were obtained from previous studies in which identical techniques for the assessment of neuromuscular blockade were used. For each group of patients the dose selected was that required just to produce complete paralysis of the tetanic response and measurements were taken once recovery had begun. It is clear that recovery from neuromuscular blockade by atracurium was appreciably faster than recovery from gallamine, fazadinium, pancuronium, tubocurarine and dimethyl tubocurarine. The rate constants for recovery of the sustained tetanus for atracurium in comparison with those calculated for known agents are shown in figure 7. Again, it is clear that recovery from neuromuscular blockade by atracurium was significantly faster than recovery from fazadinium, tubocurarine, gallamine, pancuronium and dimethyl tubocurarine.

Influence of changes in arterial pH. In the five patients studied initial underventilation increased the carbon dioxide tension to the range of 5.87–9.15 mm Hg and reduced pH to a range of 7.248–7.368 (table VI). After hyperventilation the carbon dioxide tension decreased to 3.48–3.92 mm Hg and the pH was increased to within 7.524–7.557. The effect on recovery of these changes is shown in table VI; the results were equivocal. In one patient recovery of the sustained tetanus was appreciably faster during hyperventilation; in two patients recovery was slightly faster, whereas in one patient it was unchanged and in the remaining patient recovery was slower during hyperventilation.

Surgical relaxation. In nine patients atracurium was given to facilitate intubation and to produce muscular relaxation during urological surgery (table VII). In six the trachea was intubated within 2 min of receiving a dose of 0.3 mg kg^{-1}; relaxation was adequate for 15–20 min and incremental doses of 0.1 mg kg^{-1} provided sufficient relax-

TABLE VI. *Rate constants for recovery from tetanic fade after neuromuscular paralysis by atracurium 0.2 mg kg^{-1} during respiratory acidosis (hypoventilation) and alkalosis (hyperventilation) in each of five anaesthetized patients*

Hypoventilation			Hyperventilation		
pH	P_{CO_2} (kPa)	Rate constant for recovery of sustained tetanus (% min^{-1})	pH	P_{CO_2} (kPa)	Rate constant for recovery of sustained tetanus (% min^{-1})
7.368	5.87	9.9	7.524	3.49	11.3
7.368	9.15	10.3	7.557	3.89	11.9
7.347	7.84	12.2	7.534	3.92	9.9
7.248	8.01	9.8	7.524	3.48	14.3
7.300	7.28	11.3	7.515	3.64	11.1

TABLE VII. *Skeletal muscular relaxation in nine patients given atracurium during urological surgery. Asterisks (*) denote those patients in whom blockade was reversed with neostigmine 5 mg, preceded by atropine 2 mg*

Operation	Duration (min)	Initial dose (mg kg^{-1})	Incremental dose (mg kg^{-1})	Total dose mg kg^{-1})	Skeletal muscular relaxation
Left nephroureterectomy*	90	0.32	0.13 0.13	0.58	Adequate
Right nephroureterectomy*	75	0.54	0.18 0.09	0.82	Good
Transurethral resection* of prostate	75	0.33	0.08	0.41	Good
Left pyelolithotomy*	90	0.30	0.10 0.13	0.53	Adequate
Ureterolysis* (minimal renal function)	120	0.62	0.21 0.21 0.10	1.14	Good
Right pyelolithotomy	75	0.30	0.10 0.10	0.50	Adequate
Left nephrectomy	165	0.62	0.10 0.10	0.80	Good
Conversion l. ureterostomy to a colonic conduit	150	0.30	0.10 0.10	0.62	Good
Left pyelolithotomy	90	0.30	0.10	0.40	Good

ation for a further 15–20 min. In the other three patients who were given 0.54–0.62 mg kg^{-1} intubation was achieved within 1 min and relaxation was satisfactory for 30–45 min. Incremental doses of 0.1 or 0.2 mg kg^{-1} extended relaxation for a further 15–45 min as required. In five of these nine patients antagonism was satisfactory with neostigmine 5 mg preceded by atropine 2 mg (one patient had minimum renal function). The other four patients were breathing adequately when the operation was completed and did not receive neostigmine.

Other observations. No significant changes were observed in the haematology or blood chemistry.

DISCUSSION

Atracurium has been shown to be a potent competitive neuromuscular blocking agent in anaesthetized man with no cardiovascular side-effects at doses required to produce neuromuscular paralysis, indicating the absence of histamine release. An i.v. dose of 0.3 mg kg^{-1} was sufficient to cause full block within 2 min when the vocal cords were relaxed and endotracheal intubation could be accomplished. Doubling the dose of the drug to 0.6 mg kg^{-1} produced complete block within 1 min and provided good intubating conditions. Statistical analyses revealed, as expected, that the onset and the duration of maximum block were dose-dependent. However, once the recovery process had begun the recovery phase proved to be independent of dose and the question arises whether this feature is unique for atracurium. Unfortunately, sufficient comparative information for known drugs in anaesthetized man is not available, but this aspect is worthy of further investigation.

Neostigmine effectively antagonized the block produced by atracurium even when given before recovery had begun. However, it is anticipated that induced antagonism may not always be necessary because of the rapid spontaneous recovery of the tetanic response. As with other competitive neuromuscular blocking agents, there was evidence that paralysis was enhanced and prolonged by anaesthetic concentrations of halothane.

An important property of atracurium is that the rate of recovery from neuromuscular blockade was distinctly faster than that from established competitive blocking agents. It has been known since the work of Masland and Wigton (1940) and from a more recent review by Foldes (1971), that competitive neuromuscular blocking agents, in addition to their action at the muscle end-plate, may also act presynaptically to reduce the output of acetycholine. In this context tetanic fade can be interpreted as a failure of the motor-nerve terminal to maintain a supply of acetylcholine to sustain a tetanic contraction. Thus, differences in the rate of recovery of the sustained tetanus may reflect the relative actions of drugs in depressing the release of the transmitter at the motor-nerve terminal. Since recovery of the sustained tetanic response was much more rapid after blockade by atracurium than the other agents examined (fig. 7), it is possible that atracurium may have substantially less effect on the motor-nerve terminal. This possibility could be investigated by means of the techniques now available for the measurement of acetylcholine release (Foldes, 1971).

Another attractive feature of atracurium is the consistent pattern which emerged when the drug was given repeatedly. The predictable response in terms of both the depth of blockade and rate of recovery could be interpreted as a lack of cumulative effects of the drug. The same consistent pattern occurred when atracurium was used to provide muscular relaxation during surgery. Although only nine patients were studied it appears that atracurium is a relatively short-acting agent. A dose of 0.3 mg kg^{-1} provided adequate relaxation for 15–20 min which could be extended by giving incremental doses or by using a larger initial dose of 0.6 mg kg^{-1}. Antagonism by neostigmine was not necessary in some patients in whom breathing returned rapidly to normal. This factor provides a distinct advantage, since we have demonstrated previously that the dose of neostigmine is critical; in excess, neostigmine will cause an acetylcholine-induced block which may persist for up to 20 min (Payne, Hughes and Al Azawi, 1980). In fact, it is possible that reports of recurarization after apparent adequate antagonism may have been attributable to overdosage with neostigmine.

Predictions based on the potency and time-course of neuromuscular blockade by atracurium in anaesthetized cats, dogs and rhesus monkeys (Hughes and Chapple, 1981) have proved accurate for anaesthetized man. It may be significant that the course of action of atracurium was similar throughout these species, whereas previous experience with other competitive blocking agents indicated that their duration of action, as in rhesus monkeys, was longer in man (Hughes, 1972). We also found in this study that neuromuscular block by the established drugs was more persistent in man than that indicated in laboratory animals during a comparative study with atracurium (Hughes and Chapple, 1981). Consequently, atracurium has a relatively shorter and more predictable action in anaesthetized man which, most likely, is a result of the mechanism of its inactivation.

The mechanism of inactivation of atracurium, however, has yet to be clearly defined, but laboratory studies are under way with labelled drug. However, experiments in anaesthetized cats indicate that it is unlikely that either the liver or the kidneys play a major role in the elimination of the unchanged drug (Hughes and Chapple, 1981). *In vitro* studies carried out by colleagues in the Central Analytical Laboratories, Wellcome Chemical Works, Dartford, have indicated two possible metabolic pathways. First, atracurium may undergo enzymic ester hydrolysis. Its *in vitro* half-life in normal human plasma was 26.0 ± 0.55 min ($n = 5$). Since a similar value of 24.5 min was obtained in atypical human plasma with deficient pseudocholinesterase, this suggests that, unlike suxamethonium, atracurium is not destroyed by this enzyme. Second, experiments in appropriate buffers have shown that atracurium also undergoes a non-enzymic decomposition by "Hofmann Elimination" which was at least three times faster at pH 7.6 than at pH 6.9 (Hughes and Chapple, 1981). Furthermore, it has been demonstrated *in vivo* in anaesthetized cats that the neuromuscular paralysing potency of atracurium was significantly reduced after the pH of the arterial blood had been increased from 7.31 to 7.63 by hyperventilation (Hughes and Chapple, 1981). When we attempted to demonstrate the "Hofmann" mechanism in five of our patients who acted as their own controls, recovery from neuromuscular blockade after atracurium was somewhat faster during hyperventilation in three of these patients. In one patient the reverse occurred and in the last patient no change was observed. However, it should be noted that the increase in pH achieved in this study was only in the range of 0.16–0.28 units, and there is also the possibility that an increase in pH may alter the rate of enzymic metabolism. Thus, the relative roles of the enzymic and non-enzymic decomposition of atracurium have yet to be determined and further studies will be undertaken for this purpose.

In conclusion, atracurium has the following advantages over currently available competitive neuromuscular blocking agents:

(a) Intubation can be accomplished within 1–2 min without increasing the dose to that causing cardiovascular effects or unduly prolonging the block.

(b) The rate of recovery from paralysis is two to five times faster than that of established competitive neuromuscular blocking agents.

(c) Rapid spontaneous recovery from competitive block can occur without the need for neostigmine. Nevertheless, paralysis is rapidly antagonized by neostigmine, even from complete block.

(d) The predictable response after administration indicates the lack of cumulative effects of the drug.

(e) It is highly selective with no cardiovascular side-effects at doses required for neuromuscular paralysis.

(f) Its inactivation is likely to be independent of hepatic and renal function and pseudocholinesterase activity.

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EVALUATION DE L'ATRACURIUM CHEZ L'HOMME ANESTHESIE

RESUME

L'atracurium est un agent de blocage neuromusculaire actif et concurrent chez l'homme anesthésié; il n'entraîne aucun effet cardiovasculaire aux doses requises pour obtenir la paralysie. L'intubation endotrachéale peut être effectuée après des doses intraveineuses de 0,6 et de 0,3 mg kg^{-1}, dans l'espace d'une et de 2 min, respectivement. La paralysie peut être facilement neutralisée par la néostigmine et on peut l'accroître par l'halothane. La réaction constante, en terme de blocage et de récupération, qui émerge lorsque le médicament est administré par paliers de 0,05 ou de 0,1 mg kg^{-1} indique l'absence d'effets cumulatifs. L'évolution de l'action de l'atracurium est très sensiblement plus courte que l'évolution des autres agents de blocage concurrent connus. Des doses de 0,3–0,6 mg kg^{-1} administrées par voie intraveineuse entraînent une relaxation adéquate pendant toute intervention chirurgicale d'une durée de 15 à 45 min. On a observé sur certains patients que la récupération était spontanée et que l'on n'avait pas à faire usage de la néostigmine. En plus de la décomposition non enzymatique par "Élimination d'Hoffmann", l'atracurium peut aussi subir une hydrolyse par ester enzymatique, mais contrairement à ce qui se passe pour le suxaméthonium, il ne peut pas être détruit par pseudocholinestérase.

BEURTEILUNG VON ATRACURIUM BEIM NARKOTISIERTEN MENSCHEN

ZUSAMMENFASSUNG

Atracurium ist ein starkes konkurrenzfähiges neuromuskuläres Blockierungsmittel im narkotisierten Menschen, ohne dass die für eine Lähmung erforderlichen Dosen kardiovaskuläre Auswirkungen haben. Eine Trachealrohreinführung kann nach intravenösen Dosen von 0,6 mg kg^{-1} in 1 Minute, und von 0,3 mg kg^{-1} in 2 Minuten durchgeführt werden Die Lähmung wird durch Neostigmin schnell aufgehoben und wird durch Halothan verstarkt. Die konsistente Reaktion im Bezug auf Blockierung und Erwachen bei Verabreichung der Droge in Teildosen zu je 0,05 oder 0,1 mg kg^{-1} zeigt das Fehlen kumulativer Wirkungen. Der Wirkungsverlauf von Atracurium war deutlich kurzer als der anderer anerkannter Blockierungsmittel. Intravenose Dosen von 0,3–0,6 mg kg^{-1} lieferten ausreichende Entspannung während des chirurgischen Eingriffes auf 15–45 Minuten. Spontanes Erwachen ohne die Verwendung von Neostigmin wurde bei manchen Patienten beobachtet. Zusätzlich zu dem nichtenzymischen Abbau durch "Hoffmannsche Ausscheidung" kann Atracurium auch eine enzymische Ester-Hydrolyse eingehen, kann aber im Gegensatz zu Suxamethonium nicht durch Pseudocholinesterase zerstört werden

EVALUACION DEL ATRACURIOM EN EL HOMBRE ANESTESIADO

SUMARIO

El atracuriom es un potente y competitivo agente de bloqueo muscular en el hombre anestesiado sin efectos cardiovasculares al nivel de las dosis necesarias para producir parálisis. La intubación endotraqueal puede llevarse a cabo después de dosis intravenosas de 0,6 y 0,3 mg kg^{-1}, en el periodo de 1 y de 2 minutos respectivamente. La parálisis se contrarresta rápidamente mediante neostigmina y se intensifica mediante halotano. La consistente respuesta, en lo tocante al bloqueo y a la recuperación, que surgió cuando se administró la droga bajo incrementos de 0,05 ó de 0,1 mg kg^{-1}, indica la ausencia de efectos acumulativos. El periodo de actividad del atracuriom fue, de forma apreciable, más corto que el de otros agentes de bloqueo reconocidos y competitivos. Dosis de 0,3–0,6 mg kg^{-1}, de carácter intravenoso, proveen una adecuada relajación por espacio de 15–45 min, durante las intervenciones quirúrgicas; en algunos pacientes se observó la recuperación espontánea sin el uso de neostigmina Además de la descomposición no enzimática, mediante la "Eliminación Hofmann", el atracuriom puede también emprender una hidrólisis enzímica de ésteres pero, a diferencia del suxametoniom, no puede destruirse mediante seudocolinesterasas.

Br. J. Anaesth. (1981), 53, 55

ADVERSE RESPONSES TO I.V. ANAESTHETICS

D. BEAMISH AND D. T. BROWN

SUMMARY

The adverse reactions to i.v. anaesthetics which occurred during a 3-yr period in one hospital were investigated. Sixteen reactions were reported; 13 of these occurred in a total of 7906 administrations of Althesin, two in 45 546 administrations of thiopentone and one in 630 administrations of methohexitone. The pathological process was identified in 10 patients. Most reactions were caused by activation of the alternate pathway for complement conversion.

Interest in adverse reactions to i.v. anaesthetic agents has increased greatly during the past 10 years and has been associated with the publication of a large number of case reports.

Clarke and others (1975) reported a series of 100 reactions classified according to the clinical presentation. However, reactions with a variety of clinical features may be the result of an identical process, frequently activation of the alternate pathway for complement conversion (Watkins, Appleyard and Ward, 1975; Watkins, Udnoon et al., 1976; Watkins, Clarke et al., 1976).

Evans and Keogh (1977) reported a retrospective study of the adverse responses to thiopentone, methohexitone, propanidid and Althesin which occurred in a large anaesthetic department during 3 years, but they were unable to identify the pathology underlying each reaction. We report a prospective survey of the frequency and causes of the adverse responses to i.v. anaesthetic agents in a large teaching hospital during the 3-yr period 1976–79.

METHOD

All anaesthetists in the Royal Infirmary of Edinburgh were asked to report details of adverse responses to i.v. anaesthesia and to obtain serial venous blood samples following the reaction, according to the plan of Watkins, Thornton and Clarke (1975, 1976). The clinical details associated with the reaction were recorded as soon as possible after the reaction. Plasma samples were sent to the Protein Reference Unit in Sheffield for immunoglobulin and complement analyses. Only adverse responses for which there was no obvious alternative explanation, other than a reaction to the induction agent, were included. Patients who received muscle relaxants were not included in this study. The total number of administrations of each induction agent in the hospital during the period of study was obtained from records kept by the Department of Anaesthetics.

RESULTS

Frequency of reactions

Sixteen of the reactions were attributed to i.v. anaesthesia. None was fatal. Thirteen of the 16 were associated with Althesin, two followed thiopentone and one followed methohexitone. No reactions to propanidid were reported. The apparent overall frequency of the reaction was 1 in 608 administrations of Althesin, 1 in 22 773 administrations of thiopentone and 1 in 630 administrations of methohexitone.

Reactions following Althesin administration

Nine of the 13 reactions occurred in female patients and 11 of the 13 patients were aged less than 35 yr (table I). Seven of 13 were either atopic or allergic (Dundee et al., 1978). Seven of 13 had received Althesin uneventfully within the previous 8 months. Only seven patients had received premedication and two of these patients were noted to be anxious before the induction of anaesthesia.

We obtained sequential venous blood samples following eight of the 13 adverse responses. Seven of these eight patients had clear evidence of alternate pathway activation of complement C3, a process which leads to histamine release. One of the eight patients showed activation of the classical pathway for complement conversion with evidence of a true immune-mediated response involving IgE. Four of the 13 patients (nos 4, 7, 11

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TABLE I

No	Age (yr)	Sex	Procedure	Pre-medication	Same anaesthetic previously and interval	Allergy or atopy	Plasma analysis, complement changes, immune abnormality
Althesin							
1	71	M	Cystoscopy	Diazepam	No	No	No sample
2	18	F	Cystoscopy	None	Althesin 3/12	Yes	C3 conversion Immunopathology
3	29	F	Dilatation and curettage	None	No	No	C3 conversion Classical pathway
4	18	M	Drainage of abscess	None	No	Yes	No sample
5	45	F	Hysterectomy	Lorazepam	Althesin 6/52	No	C3 conversion Memory
6	19	F	Ovarian cystectomy	Lorazepam	Althesin 1/52	Yes	C3 conversion Memory
7	33	M	Drainage of abscess	None	No	Yes	C3 conversion Immunopathology
8	22	F	Termination of pregnancy	Lorazepam	No	No	No sample
9	35	F	Termination of pregnancy	Diazepam	Althesin 3/12	No	C3 conversion IgE involved
10	19	F	Termination of pregnancy	Lorazepam	No	Yes	No sample
11	22	M	Drainage of abscess	None	Althesin 2/52	No	No sample
12	28	F	Dilatation and curettage	Lorazepam	Althesin 8/12	Yes	C3 conversion Immunopathology
13	23	F	Insertion of I.U.C.D	None	Althesin 6/12	Yes	C3 conversion IgE involved
Thiopentone							
14	23	F	Termination of pregnancy	None	No	No	C4 increased Immunopathology
15	38	F	Laparoscopic sterilization	Hyoscine	No	No	C4 increased C2 kinin release
Methohexitone							
16	33	M	Drainage of abscess	None	No	Yes	No sample

and 13) had a history of chronic infection. One patient who had chronic axillary abscess cavities requiring repeated surgical drainage reacted in an identical manner to both Althesin and methohexitone on separate occasions.

In three patients the anaesthetist had administered a test dose of Althesin 0.5 ml i.v. without adverse effects, although subsequently an adverse response occurred following injection of the full induction dose of Althesin.

Reactions following thiopentone administration

Only two reactions occurred following the administration of thiopentone (table I). These were investigated immunologically and showed that both patients had increased concentrations of complement C4. The complement concentrations did not change following the reactions, so it is not clear to what extent this underlying immunopathology contributed.

Reactions following methohexitone administration

Only one patient had an adverse reaction after receiving methohexitone. The patient had a history of recurrent abscesses and reacted adversely to Althesin during a subsequent anaesthetic.

Reactions following propanidid administration

No reactions were reported following 629 administrations of propanidid.

DISCUSSION

The results show that adverse reactions involving Althesin (13 in 7904) occur more frequently than reactions to thiopentone (2 in 45 546). The frequencies for methohexitone (1 in 630) and propanidid (0 in 629) are of doubtful significance because these drugs were used so infrequently. Adverse reactions to anaesthetics are probably always under-reported and so the frequencies we have calculated are possibly less than the true frequencies. Scott (1979) reported a frequency of 1 in 430 reactions following Althesin and other estimates have ranged from 1 in 930 (Evans and Keogh, 1977) to 1 in 19 000 (Clarke et al., 1975).

Watkins (1979) described four pathological mechanisms which lead to an adverse clinical response to i.v. anaesthetics. The first was the combination of an antigenic drug with reaginic immunoglobulin IgE (true anaphylaxis); the second was activation of the classical pathway for the conversion of complement C3; the third was activation of the alternate pathway for C3 conversion and the fourth was pharmacological or chemical release of histamine. Conversion of complement C3 to its breakdown products releases C3a (anaphylatoxin) which is a potent releaser of stored histamine (Ruddy, Gigh and Austen, 1972).

After the administration of Althesin, seven of our patients showed alternate pathway conversion of complement and two of these also showed involvement of IgE.

Three patients in the series suffered from chronic infections. This form of immunopathology appears to sensitize the complement pathway. One of the patients reacted to different drugs on two separate occasions, once following methohexitone and once following Althesin (Beamish and Brown, 1980).

Five of the patients who reacted to Althesin had received the drug on a previous occasion within the preceeding 3 months. Patients receiving repeated doses of Althesin appear to have an increased risk of adverse reactions. This has been confirmed by experimental work in the "miniature" pig (Glen et al., 1978), which showed that the optimum interval between Althesin injections for provoking adverse reactions was between 1 and 2 weeks. Watkins, Allen and Milford Ward (1979) have reported a patient in whom immunoglobulin IgD appeared to be the cause of a short-term "immunological memory" response following the repeated administration of Althesin.

Two patients had a delayed adverse response following Althesin. The first developed skin weals after 5 h and the second developed erythema, hypotension and bronchospasm after 90 min. It is difficult to explain such a delay, either on the basis of a reaction to a metabolite of Althesin or by variations in the speed of reaction of the complement pathway. Nevertheless, the delay has great significance for anaesthetized outpatients, who may be discharged before they develop symptoms.

There were no deaths attributable to the 16 reactions we have described. Our data suggest that the possibility of an adverse reaction to Althesin is more than 30 times that to thiopentone and we suggest that this should be borne in mind when selecting an i.v. agent.

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REACTIONS ADVERSES AUX AGENTS ANESTHESIANTS ADMINISTRES PAR VOIE INTRAVEINEUSE

RESUME

Les réactions adverses aux agents anesthésiants administrés par voie intraveineuse que l'on a enregistrées au cours d'une période de trois ans, dans un même hôspital, ont fait l'objet de recherches. Seize réactions ont été signalées, 13 d'entre-elles se sont produites sur un total de 7906 administrations d'Althésine, deux sur un total de 45 546 administrations de thiopentone et une sur 630 administrations de méthohéxitone Le processus pathologique a été identifié sur 10 patients. La plupart des réactions avaient été causées par une activation de l'autre voie d'accès pour conversion du complément.

UNGÜNSTIGE REAKTIONEN AUF INTRAVENÖSE ANÄSTHESIE

ZUSAMMENFASSUNG

Die ungünstigen Reaktionen auf intravenose verabreichte Anästhesiemittel, zu der es während einer dreijährigen Periode in einem Krankenhaus kam, wurde untersucht. Sechzehn solche Reaktionen wurden gemeldet; 13 davon erfolgten bei insgesamt 7906 Injektionen von Althesin, zwei bei 45 546 Injektionen von Thiopenton, und eine bei 630 Methohexiton-Injektionen. Der pathologische Prozess wurde in 10 Patienten Identifiziert. Die meisten dieser Reaktionen wurden durch Aktivierung des alternativen Leitweges fur Komplementumwandlung verursacht.

REACCIONES ADVERSAS A LOS ANESTESICOS INTRAVENOSOS

SUMARIO

Se investigaron las reacciones adversas a los analgésicos intravenosos, las cuales tuvieron lugar durante un periodo de 3 años en un hospital. Se notificaron 16 reacciones; 13 de éstas ocurrieron en un total de 7906 administraciones de Altesín, otras 2 en un total de 45 546 administraciones de tiopentona y 1 en 630 administraciones de metohexitona Se identificó el proceso patológico en 10 pacientes, la mayoria de las reacciones fueron causadas por la activación de la ruta alternativa para la conversión del complemento.

Br. J. Anaesth. (1981), 53, 59

WY 16225 (DEZOCINE), A NEW SYNTHETIC OPIATE AGONIST-ANTAGONIST AND POTENT ANALGESIC: COMPARISON WITH MORPHINE FOR RELIEF OF PAIN AFTER LOWER ABDOMINAL SURGERY

J. W. DOWNING, J. G. BROCK-UTNE, A. BARCLAY AND I. L. SCHWEGMANN

SUMMARY

Dezocine (Wy 16225), a new analgesic was compared randomly and double-blind with morphine 10 mg in 160 female patients complaining of moderate (group I) or severe (group II) pain after elective lower abdominal surgery; both drugs were given i.m. In group I, pain relief with dezocine 10 and 15 mg was significantly greater than dezocine 5 mg; dezocine 10 mg appeared equipotent with morphine 10 mg. Similar, but statistically insignificant differences were observed in group II. Patient sedation was minimal and untoward side-effects infrequent with all doses of the trial drugs.

A double-blind comparison of the efficacy and safety of dezocine, a new synthetic opiate agonist–antagonist (Wyeth Laboratories), in a range of doses (5, 10 and 15 mg) was made with morphine 10 mg after elective lower abdominal surgery. (The study was authorized by the Medicines Control Council of South Africa and approved by the Ethical Committee for human investigations of the Faculty of Medicine, University of Natal.)

MATERIALS AND METHODS

One hundred and sixty African females, ASA status I-II aged 15–50 yr, were studied after major elective lower abdominal surgery. The purpose, methods and risks of the study were explained to each patient at the preoperative visit, and their informed consent obtained. All pre-anaesthetic interviews and subsequent observations and recordings after surgery were conducted by a single observer (I. L. S.). Pregnant women and any patient receiving a potent analgesic or with a history of chronic opiate abuse were excluded.

One hundred and forty-seven patients underwent elective Caesarean section and received no pre-anaesthetic analgesic or ataractic medication. The remaining 13 women were given diazepam 5–10 mg i.m. 1 h before surgery. Anaesthesia was induced with thiopentone 3.5 mg kg^{-1} i.v. and maintained with 40–50% nitrous oxide in oxygen and a volatile agent (0.5% halothane or 1.0% enflurane). The lungs were mechanically ventilated throughout the procedure. Muscle relaxation was achieved with alcuronium 0.2 mg kg^{-1} i.v. Administration of analgesic or neuroleptic agents was avoided during anaesthesia.

After operation, in the recovery room, patients were allocated initially to two groups, depending on whether they reported moderate (group I, 80 patients) or severe (group II, 80 patients) pain when questioned on wakening from anaesthesia. To enter the study, a patient had to express the need for pain relief and was then encouraged to wait approximately 15 min. Those patients who thereafter no longer expressed a need for analgesia were excluded from the study. The remainder were given i.m. injection of a test drug.

The patients were further subdivided, using separate randomization tables for groups I and II, into four dose groups (a, b, c and d) with 20 patients in each. Patients received dezocine 5 mg (a), dezocine 10 mg (b), dezocine 15 mg (c), or morphine sulphate 10 mg (d). All drugs were dissolved in 1 ml of solution but not presented in identical ampoules. Therefore, before drug administration, all drugs were initially drawn into a 2-ml syringe by the anaesthetist and handed to the observer for subsequent i.m. injection. The solutions of the test drugs had an identical appearance in the syringe. Neither the patient nor the observer (I. L. S.) was aware of the nature, or dose of the drug given.

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Details of the drug used and dose given to each patient were entered by the anaesthetist into both the drug register and the patient's clinical record. The observer recorded the patient's name, hospital and drug ampoule numbers on a separate data sheet before injection of the drug. The patient's chart and double-blind code were available only to the anaesthetist prescribing the postoperative analgesic.

Evaluations of pain relief were made by requesting the patient to judge whether the injection had provided complete (4 points), more than 50% (3 points), equal to 50% (2 points), less than 50% (1 point), no pain relief (0 points), or pain worse than before (−1 point), with a high point score denoting good analgesia and a low value, inadequate pain relief. Simultaneously, an assessment of the degree of patient sedation present was made by the observer on the basis of none, mild, moderate or marked, designated 1–4, a high score indicating significant and a low value minimal sedative effect. Further evaluations of pain relief and sedation were conducted at 15 and 30 min, then 1, 2 and 4 h after analgesic administration.

Patients with less than 50% pain relief at 30 min were encouraged to wait an additional 30 min. If the response remained the same 1 h after drug injection, the patient was given morphine sulphate, with dose adjusted according to body weight and to compensate for the antagonist affect of dezocine to morphine. The study was then considered complete in that patient.

Systolic and diastolic arterial pressures, heart and breathing rates, were recorded at each evaluation. Side effects observed during the study were noted. The results obtained were submitted for statistical analysis using appropriate tests for parametric and non-parametric data by the Biostatistics Department of Wyeth Laboratories (U.S.A.).

RESULTS

The average age, mean body weight and height of the patients in each of the four dosage series (a, b, c and d) and in groups I and II, were comparable except for patients in group I given dezocine 15 mg and morphine 10 mg (series c and d), who were taller ($P<0.05$).

Analyses of the pain relief score averages in group I using Kruskal–Wallis chi-square test corrected for ties (Siegel, 1956), shown in table I and supplemented for pair comparison by Dunn's multiple comparison procedure (Dunn, 1964) showed that dezocine 5 mg was significantly less effective than both dezocine 10 mg at 30 min ($P<0.05$), and dezocine 15 mg at 2 and 4 h ($P<0.05$). No statistically significant differences were noted between dezocine 10 and 15 mg, or between dezocine 5, 10, 15 mg and morphine 10 mg. Similar, but insignificant trends were noted in group II.

Comparison of the proportions of patients with effective ($\geqslant 50\%$) pain relief at each observation in the two broad categories using the Chi-square test and Fishers's exact test for pair comparison supplemented those findings (table II). In group I, dezocine 10 mg was more effective than dezocine 5 mg at 4 h ($P<0.05$), dezocine 15 mg more effective than dezocine 5 mg at 1, 2 h ($P<0.05$) and 4 h ($P<0.01$), and dezocine 15 mg more effective than morphine 10 mg at 2 h ($P<0.01$).

Latency of onset of effective pain relief was slightly shorter after dezocine 10 and 15 mg injections compared with morphine 10 mg and dezocine 5 mg in groups I and II (table III), but no statistical differences in latency of onset of analgesia were demostrated in either group.

Duration of analgesic action apparently increased with the dose of dezocine in both groups. The shortest duration of effective pain relief was seen after injection of dezocine 5 mg, morphine 10 mg being intermediate between dezocine 5 and 10 mg (table III).

No significant increase in sedation was noticed with any drug regimens except for two patients in group II who consistently were more sedated after administration of analgesia. Sedation score average showed a steady reduction from baseline throughout the study period.

Systolic, diastolic and pulse pressures, and heart and breathing rates remained stable throughout the investigation in both major groups. None of the few changes noted in these measurements was considered clinically significant.

Only six of the 160 patients studied experienced adverse side-effects. Two patients were nauseated and vomited after receiving dezocine 5 mg and morphine 10 mg respectively.

One patient in each of the following treatment series suffered nausea after drug administration: dezocine 10 mg, 15 mg and morphine 10 mg. No significant difference in the frequency of side-effects was demonstrated between the four treatment regimens of groups I and II.

TABLE I. *Pain relief score averages.* n = 20 *for each treatment.* (K *value is the Kruskal–Wallis chi-square connected for ties (Siegel, 1956). *Statistically significant at 0.05 level. Scoring of pain relief: Complete = 4; more than 50% relief = 3; 50% relief = 2; less than 50% relief = 1; no relief = 0. High score indicates good analgesia. Pain worse = −1*

Group	Treatment series	Time after therapy				
		15 min	30 min	1 h	2 h	4 h
Group I (moderate pain)	(a) dezocine 5 mg	0.4	0.8	1.3	1.1	0.5
	(b) dezocine 10 mg	0.8	1.5	1.7	1.5	1.1
	(c) dezocine 15 mg	0.7	1.4	1.9	2.0	1.5
	(d) morphine 10 mg	0.5	0.9	1.4	1.3	0.8
	K value	5.021	11.133*	6.446	8.244*	11.288*
	P value	0.170	0.011	0.092	0.041	0.010
Group II (severe pain)	(a) dezocine 5 mg	0.4	0.8	1.1	0.7	0.5
	(b) dezocine 10 mg	0.5	1.0	1.5	1.4	1.1
	(c) dezocine 15 mg	0.5	1.0	1.4	1.6	1.2
	(d) morphine 10 mg	0.4	0.9	1.5	1.4	1.0
	K value	1.010	1.614	2.522	7.270	5.053
	P value	0.799	0.656	0.471	0.064	0.168

TABLE II. *Percentage patients with effective pain relief* (≥50%) n = 20 *for each treatment. *Statistically significant at 0.05 level*

Group	Treatment series	Time after therapy				
		15 min	30 min	1 h	2 h	4 h
Group I (moderate pain)	(a) dezocine 5 mg	5.0	15.0	35.0	45.0	5.0
	(b) dezocine 10 mg	5.0	45.0	65.0	55.0	35.0
	(c) dezocine 15 mg	10.0	35.0	75.0	85.0	50.0
	(d) morphine 10 mg	0.0	20.0	55.0	40.0	25.0
	χ^2 value	2.105	5.533	7.161	9.905*	10.435*
	P value	0.551	0.136	0.067	0.019	0.1015
Group II (severe pain)	(a) dezocine 5 mg	0.0	15.0	45.0	30.0	15.0
	(b) dezocine 10 mg	0.0	25.0	55.0	55.0	40.0
	(c) dezocine 15 mg	0.0	30.0	50.0	70.0	45.0
	(d) morphine 10 mg	0.0	15.0	50.0	50.0	35.0
	χ^2 value	0.000	2.017	0.400	6.554	4.786
	P value	1.000	0.569	0.940	0.088	0.188

TABLE III. *Mean latency of onset and duration of effective pain relief* (≥50%) (*min*). **Conditional arithmetic mean time of onset and conditional mean duration calculations based on data only from patients reporting effective pain relief. **Unconditional harmonic time of onset and overall mean duration computations include data from patients never obtaining effective relief*

Group	Treatment series	Time of onset of analgesia		Duration of effective pain relief	
		*Arithmetic mean	**Harmonic mean	*Conditional mean	**Overall mean
Group I (moderate pain)	dezocine 5 mg	68	89	132	66
	dezocine 10 mg	54	44	146	132
	dezocine 15 mg	57	44	200	180
	morphine 10 mg	55	77	159	95
Group II (severe pain)	dezocine 5 mg	50	100	153	69
	dezocine 10 mg	53	73	211	126
	dezocine 15 mg	68	65	195	146
	morphine 10 mg	57	89	194	107

DISCUSSION

Estimation of the analgesic potency of a drug requires some immediate measure of the presence or absence of pain by initial patient judgement of its severity (Houde, Wallenstein and Rogers, 1960). Our primary allocation of subjects to two broad categories was based on each patient's subjective assessment of the degree of pain suffered immediately upon wakening from the anaesthetic.

The system of pain relief assessment used in this study is a modification of the quantal methods for the measurement of analgesic effect described by Beecher (1957) and by Swerdlow, Murray and Daw (1963), and is less popular than the more quantitative scale of pain relief or intensity (none, slight, moderate, marked or severe). However, provided the relative effects of the test medications under scrutiny are compared, results obtained using qualitative or quantitative measures of analgesic efficacy should not differ greatly (Houde, Wallenstein and Rogers, 1960).

The pain relief score average obtained from two primary categories in this study, were similar (table I). However, the percentage of patients with effective pain relief (≥ 50%) at various times after medication (table II) was less in group I compared with group II, suggesting the value of previous classification of patients into moderate and severe pain groups. Although statistically significant differences between the four treatment groups (a, b, c and d) only emerged in the moderate pain group, a similar trend was apparent in the severe pain category. Statistically important differences might have been revealed in group II by increasing the number of subjects studied in each of the four treatment groups.

Dezocine, a new agonist–antagonist analgesic, is structurally related to pentazocine (fig. 1). A 2% aqueous solution has pH 4.6. Latency of onset, analgesic potency and duration of action of the new drug appear similar to morphine. In rats, dezocine has 0.56 the potency of nalorphine as an antagonist to morphine. The cardiovascular effects of dezocine in dogs are insignificant and the drug produces minimal respiratory depression in monkeys (Investigator's confidential brochure, Wy 16225, Wyeth Laboratories).

Fragen and Caldwell (1978) compared dezocine 5 and 10 mg with pethidine 25 and 50 mg in a double-blind randomized clinical trial. It was conducted in 187 patients with and without premedication after a variety of surgical operations. The two test drugs produced comparable degrees of pain relief and sedation. Changes in vital signs and the frequency of side-effects after the injection of dezocine and pethidine were similar and clinically insignificant. These authors concluded that dezocine 10 mg and pethidine 50 mg were equipotent. Dezocine was not associated with nallorphine-like psychomimetic phenomena sometimes encountered after pentazocine administration (Goodman and Gillman, 1975).

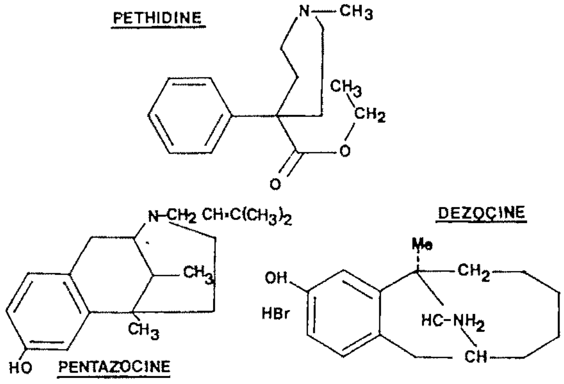

FIG. 1 Structural formulae

This study indicates that dezocine is efficient and safe for the relief of moderate pain after lower abdominal obstetric or gynaecological surgery. Dezocine 10 mg provided analgesia equivalent to morphine 10 mg by injection. Dezocine 10 mg thus appeared more potent in the present study than in that of Fragen and Caldwell (1978) in that morphine is considered to be 8–10 times more potent than pethidine. The analgesic efficacy of dezocine was enhanced by increasing the dose to 15 mg. Changes in systolic and diastolic pressure and heart respiratory rate were of no clinical significance.

Our patients were minimally sedated immediately after awakening from general anaesthesia. This could be related to the administration of premedication to only 13 of the 160 patients studied, the use of low concentrations of volatile agents and the exclusion of potent analgesic or ataractic drugs from the anaesthetic maintenance technique. Neither dezocine 5, 10 and 15 mg, nor morphine 10 mg produced increased sedation.

The frequency, of side-effects recorded after dezocine and morphine was small, but our clinical experience (Downing, Leary and White, 1971), and the unpublished results of a pilot study conducted in this department suggest that emesis after operation occurs infrequently in the African patient.

Undesirable psychological reactions may follow the administration of pentazocine (Goodman and Gillman, 1975). Despite dezocine's obvious structural relationship to pentazocine, no psychomimetic phenomena were observed after dezocine injection by either Fragan and Caldwell (1978) or ourselves. Parenteral administration of pentazocine may produce dependence in man (Goodman and Gillman, 1975). Dezocine neither substitutes for morphine nor produces direct dependence when administered chronically to monkeys (Investigators confidential brochure, Wy 16225). The potential for dezocine abuse by man is as yet unknown.

If clinical trials in man substantiate animal results, this new analgesic may be a useful substitute for morphine and pethidine.

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Wy 16225 (DEZOCINE), NOUVEL ANALGESIQUE PUISSANT, SYNTHETIQUE, OPIACE, AGONISTE ET ANTAGONISTE: COMPARAISON AVEC LA MORPHINE POUR LE SOULAGEMENT DE LA DOULEUR APRES INTERVENTION CHIRURGICALE DANS LE BAS DE L'ABDOMEN

RESUME

La dézocine (Wy 16225) est un nouvel analgésique que l'on a comparé, au cours d'une étude à double inconnue faite au hasard, à la morphine en doses de 10 mg administrées à 160 femmes se plaignant de douleurs modérées (group I) ou fortes (group II) après une intervention chirurgicale à froid, dans la partie inférieure de l'abdomen; ces deux médicaments ont été administrés par voie intramusculaire. Dans le groupe I, le soulagement de la douleur à l'aide de la dézocine en doses de 10 et 15 mg a été sensiblement plus grand que celui apporté par la dézocine en doses de 5 mg; la dézocine, en doses de 10 mg, semble être équipotente à 10 mg de morphine. On a observé des différences similaires, mais insignifiantes du point de vue statistique, dans le group II. La sédation des patients est restée minimale et les effets secondaires rebelles ont été peu fréquents avec toutes les doses de médicaments utilisés pour les essais

WY 16225 (DEZOCIN), EIN NEUER SYNTHETISCHER OPIAT-AGONIST/ANTAGONIST UND EIN STARKES ANALGETIKUM. VERGLEICH MIT MORPHIUM ZUR SCHMERZLINDERUNG NACH UNTERLEIBSEINGRIFFEN

ZUSAMMENFASSUNG

Dezocin (Wy 16225), ein neues Analgetikum, wurde willkürlich und doppelblind mit einer Dosis von 10 mg Morphium verglichen—bei 160 Patientinnen, die über massige (Gruppe I) und schwere (Gruppe II) Schmerzen nach elektiven Unterleibsoperationen klagten; beide Drogen wurden intramuskulär verabreicht. In Gruppe I war die Schmerzlinderung mit 10 und 15 mg Dezocin wesentlich starker als mit 5 mg Dezocin; 10 mg Dezocin schienen gleichstark wie 10 mg Morphium zu wirken. Ähnliche, aber statistisch unbedeutende Unterschiede wurden in Gruppe II festgestellt. Die Patientinnen waren minimal sediert, und unerwunschte Nebenerscheinungen waren bei allen Dosen der Versuchsdrogen selten.

Wy 16225 (DEZOCINA), UN NUEVO OPIATO SINTETICO AGONISTA-ANTAGONISTA Y UN POTENTE ANALGESICO: COMPARACION CON LA MORFINA EN LO TOCANTE AL ALIVIO DEL DOLOR DESPUES DE INTERVENCION QUIRURJICA EN LA PARTE BAJA DEL ABDOMEN

SUMARIO

La dezocina (Wy 16225), que es un nuevo analgésico, se ha comparado al azar y mediante métodos de doble anonimato con 10 mg de morfina en 160 pacientes femeninos que se quejaban de dolor lijero (grupo I) o agudo (grupo II), después de intervención quirúrjica de la parte baja del abdomen; ambas drogas se administraron con carácter intramuscular. En el

grupo I, el alivio del dolor mediante 10 y 15 mg de dezocina fue significativamente superior al obtenido con 5 mg de dicho compuesto; 10 mg de dezocina se presentaron como equipotentes a 10 mg de morfina. Así mismo, se observaron diferencias estadísticas insignificantes en el grupo II La sedación de los pacientes fue mínima y los efectos secundarios adversos no fueron frecuentes en todas las dosis de las drogas bajo prueba.

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E.E.G. ACTIVITY DURING HALOTHANE ANAESTHESIA IN MAN

E. OSHIMA, K. SHINGU AND K. MORI

SUMMARY

The effects of i.v administration of suxamethonium and noxious stimulation induced by skin incision on the e.e.g. were studied during halothane anaesthesia in man These stimuli induced activation of the e.e.g. which was represented by either low-voltage fast waves or high-voltage slow waves The low-voltage fast wave response was observed in adult patients while the high-voltage slow wave response was the predominant response in infants and children aged less than 8 yr Suxamethonium induced the high-voltage slow wave response in 77% of cases, skin incision in 88%. The e e g. of four infants aged less than 60 days did not show activation with either stimulus. Both types of e.e g. activation were associated with an increase in heart rate, increase in arterial pressure and pupillary dilatation. The possible mechanisms involved in the production of activation of e.e.g. by i.v. administration of suxamethonium are discussed

Transition from sleep to wakefulness or from relaxation to alertness is accompanied by a change from high-voltage slow waves (HVS) on e.e.g. to low-voltage fast waves (LVF). Moruzzi and Magoun (1949) demonstrated that high frequency stimulation of midbrain tegmentum in isolated cat brain preparations, and of peripheral nerves in cats given small doses of chloralose, induced this change in the e.e.g. These effects have been confirmed by numerous investigators, such as Arduini and Arduini (1954) and Killam and Killam (1958), using different anaesthetics. However, Prince and Shanzer (1966) and Kaada and others (1967) showed that such stimulation in anaesthetized cats sometimes produced HVS, rather than LVF.

One of us reported previously that changes in e.e.g. could also be induced in man during light halothane anaesthesia by skin incision or i.v. administration of suxamethonium (Mori Iwabuchi and Fujita, 1973). It was reported that the e.e.g. pattern of activity could be either LVF or HVS and that LVF responses were induced in adult patients while HVS occurred in infants and young children. Bimar and Bellville (1977) described these two types of e.e.g. activity induced by noxious surgical manipulation during light anaesthesia in man. However, they did not discuss factors which determined the type of e.e.g. pattern induced in individual patients.

In this study an attempt was made to confirm our previous suggestion that the age of patient is the main factor determining the type of e.e.g. activity during halothane anaesthesia in man.

METHODS

Sixty-two patients were studied. Informed consent was obtained at the preoperative visit from all adult patients and the parents of infants and children. Patients with cardiovascular, respiratory or neurological disorders were not included. No premedication was given. Anaesthesia was induced with 2.5–3.0% halothane in oxygen. After induction the larynx and trachea were sprayed with 4% lignocaine and the trachea was intubated. The concentration of halothane was then reduced to 0.5–0.75%.

A continuous monopolar (ear as reference point) or bipolar e.e.g. was recorded with an eight-channel recorder (Nihon-Koden EEG-7109). The electrodes were 27-gauge subdermal needles. The high frequency filter was set at "off" and the low frequency filter at time constant 0.1 s. E.c.g. lead II was recorded simultaneously on one channel.

Ten to 15 min after intubation, suxamethonium 1 mg kg^{-1} was administered i.v. and the e.e.g. was monitored for 10 min. Approximately 10 min later when the preparations for operation were complete, alcuronium 0.2 mg kg^{-1} was administered i.v., the skin incision made and effects of surgically-induced noxious stimulation on e.e.g. were observed. Breathing was assisted before administration of the muscle relaxants and then controlled manually.

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RESULTS

Data were collected from 56 patients in whom e.e.g. recordings were obtained successfully. The e.e.g. responses of individual patients induced by the two types of stimulation are shown in table I. Forty-two patients showed activation of e.e.g. following suxamethonium i.v., 11 showed no response and in three the recordings were unsatisfactory because of artefacts. In the same group of patients, 35 showed e.e.g. activation following skin incision, 15 no response and in six there were artefacts. Records containing artefacts were discarded.

The e.e.g. responses were either low-voltage fast waves (LVF) or high-voltage slow waves (HVS). They occurred several seconds after the appearance of muscle fasciculations following suxamethonium or skin incision and returned to the pre-stimulation pattern within 5–10 min if no further stimulation was applied. HVS response was sometimes preceeded (fig. 1) and always followed by LVF pattern of varying degree (fig. 2). The HVS response was not uniform on visual inspection but could be classified. The characteristics of the responses were as follows.

LVF ("desynchronization")

LVF response was represented by a change in e.e.g. activity from high-voltage (10–12 Hz) to low-voltage (14–20 Hz) waves, which was similar to the e.e.g. pattern known as the arousal or desynchronization of cortical activity in the cat (Moruzzi and Magoun, 1949) (fig. 3).

HVS ("synchronization")

HVS response could be classified by the frequency of e.e.g. activity into four types as follows.

Delta wave type. This type of response was characterized by a sudden appearance of 1.5–4 Hz sinusoidal rhythmic activity (fig. 1). LVF activity was always found to be superimposed on the slow waves. When the slow waves disappeared, the fast wave component became dominant and the typical "desynchronization" was noted.

Theta and delta wave type. This response was characterized by the mixture of delta (0.5–3 Hz) and theta (4–7 Hz) activity. E.e.g. activity was more irregular and the rhythmicity less dominant than in the other types of HVS response (fig. 2).

TABLE I. *Patients and results. NR = no response induced by stimulation, — = record spoiled by artefact; LVF = low voltage fast wave response induced by stimulation; δ = delta wave type activation; θ = theta wave type activation; θ,δ = theta and delta wave type activation; α = alpha wave type activation*

Patient no.	Suxamethonium	Skin incision	Age (yr	mth	d)
1	NR	NR			25
2	NR	NR			40
3	NR	NR			40
4	NR	NR			54
5	—	—		2	
6	LVF	LVF		3	
7	—	—		3	
8	—	—		3	
9	—	θ		4	
10	NR	δ		4	
11	δ	δ		6	
12	NR	δ		6	
13	δ	NR		10	
14	NR	NR	1		
15	θ, δ	θ, δ	1		
16	α	θ, δ	1	1	
17	δ	θ	1	2	
18	—	θ	1	2	
19	δ	θ	1	4	
20	δ	NR	1	6	
21	α	α	1	7	
22	δ	δ	1	7	
23	—	θ	1	11	
24	θ	θ	2	6	
25	θ, δ	θ, δ	2	8	
26	θ	θ	2	10	
27	NR	NR	2	10	
28	δ	θ, δ	2	11	
29	θ	—	3		
30	δ	θ	3	8	
31	LVF	—	3	10	
32	NR	NR	4	3	
33	θ, δ	—	4	4	
34	δ	δ	4	7	
35	LVF	θ	4	8	
36	α	θ	4	10	
37	LVF	NR	5		
38	δ	NR	5	8	
39	α	α	5	8	
40	α	α	5	10	
41	LVF	NR	6	4	
42	δ	δ	6	7	
43	LVF	LVF	7		
44	δ	NR	7		
45	δ	δ	7		
46	LVF	LVF	7	1	
47	—	—	7	2	
48	NR	NR	7	6	
49	LVF	LVF	8	4	
50	LVF	LVF	8	8	
51	LVF	LVF	8	10	
52	NR	NR	9	2	
53	LVF	—	9	5	
54	LVF	—	10		

TABLE I (*cont.*)

Patient no.	Suxamethonium	Skin incision	Age (yr	mth	d)
55	—	—	11		
56	LVF	LVF	15	1	
57	—	—	26		
58	LVF	LVF	29		
59	LVF	LVF	38		
60	LVF	—	44	3	
61	LVF	LVF	46		
62	LVF	LVF	48	2	

Theta wave type. This was characterized by rhythmic smooth sinusoidal high voltage e.e.g. of 4–7 Hz (fig. 4).

Alpha wave type. This was characterized by high voltage (10–12 Hz) activity, similar to the so-called barbiturate spindle bursts (fig. 5).

When the e.e.g. responses were induced by both types of stimulation, the durations were not equal. When both stimuli induced HVS responses, the occurrence of HVS and LVF activity in the responses and the types of HVS activity were not always identical (table I). Therefore, the classification of e.e.g. response was based essentially on the presence or absence of HVS waves. Responses consisting only of LVF waves were classified as LVF responses. Those containing HVS waves of more than 10 s duration were classified as HVS responses even if the remainder of the response consisted of LVF waves.

Using these criteria, the e.e.g. responses were examined following suxamethonium and skin incision in 30 patients. Eleven (37%) showed LVF responses and 18 (60%) HVS responses following both stimuli and one (3%) the LVF response after suxamethonium and the HVS response after skin incision (table II).

Thirty-seven patients aged less than 8 yr showed either LVF or HVS response, or both, while the 12 older patients showed only the LVF response (table I). Of the younger group of 37 patients, 31 had e.e.g. activation after suxamethonium, 24 (77%) showing the HVS response and 7 (23%) the LVF response (table III). Twenty-six of the same group of patients showed e.e.g. activation by skin incision, 23 (88%) showing the HVS response and 3 (12%) the LVF response (table III).

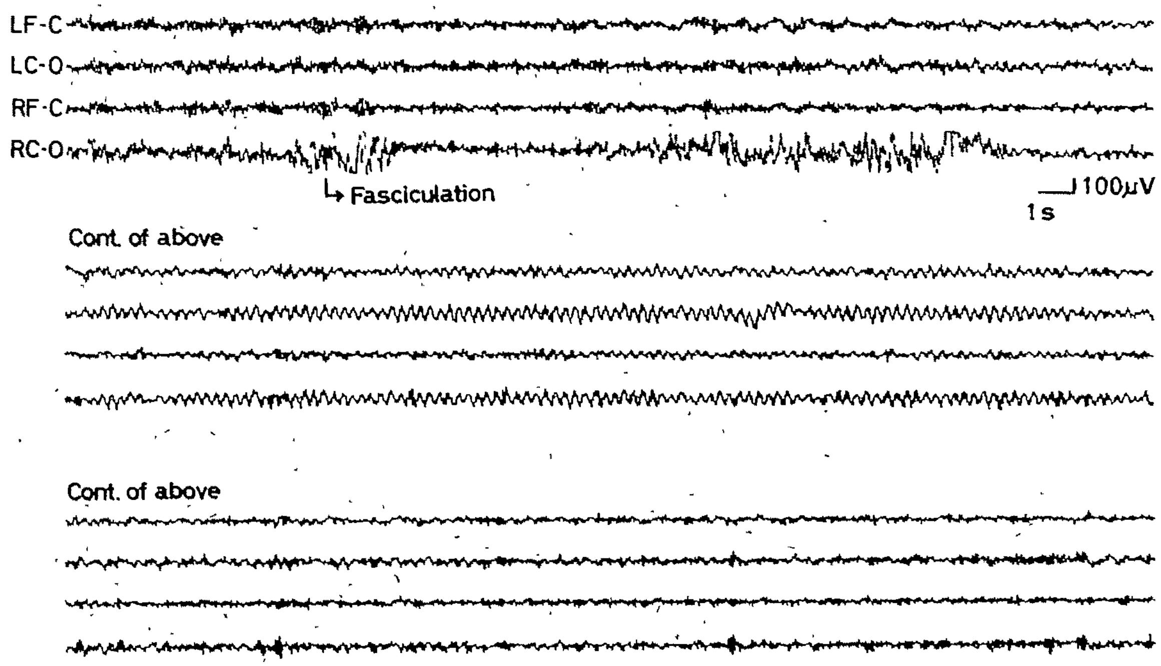

FIG. 1. Delta wave type of e.e.g. activity induced by suxamethonium 1 mg kg^{-1} i.v. in a patient aged 4 yr 7 months (patient no. 34). The e.e.g. of halothane anaesthesia is replaced by LVF several seconds after the appearance of muscle fasciculations, followed by rhythmic sinusoidal 3.5–4 Hz activity. The sinusoidal activity is then followed by LVF activity.

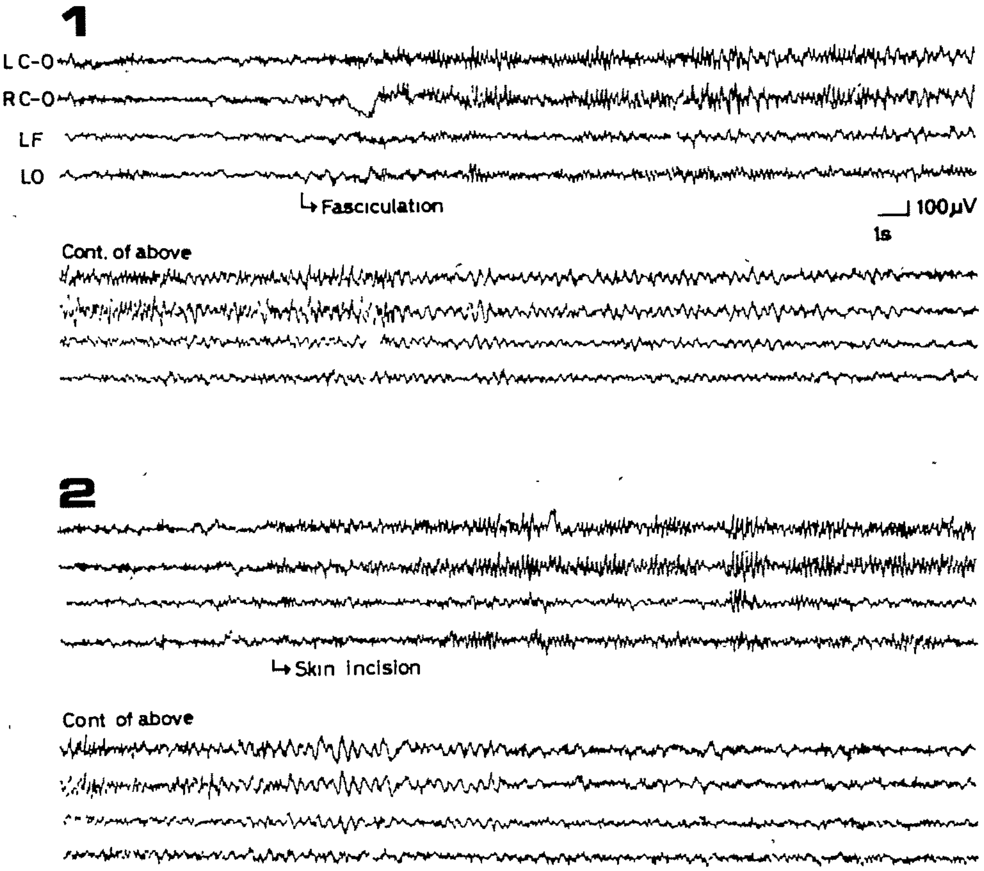

FIG. 2 Comparison of e.e.g. activity induced by suxamethonium i.v. and noxious stimulation induced by skin incision in a patient aged 2 yr 8 months (patient no. 25). 1: Effects of suxamethonium 1 mg kg^{-1} i.v. Several seconds after the appearance of muscle fasciculations, theta waves occur and then delta band high-voltage activity. The HVS waves are followed by LVF waves seen at the last part of the trace 2. Effects of skin incision in the same patient. The record was obtained 20 min after 1 above. The changes in e.e.g. are similar to those induced by suxamethonium.

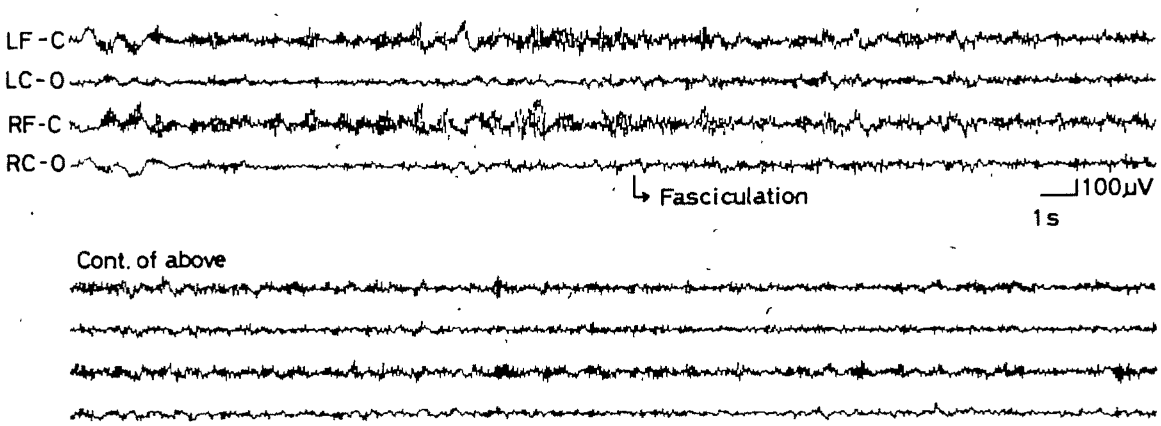

FIG. 3 LVF type of e.e.g. activity induced by suxamethonium 1 mg kg^{-1} i.v. in a patient aged 9 yr 5 months (patient no. 53). Before the appearance of muscle fasciculations, the e.e.g. shows 10–12 Hz HVS waves which are replaced by LVF waves of 15–20 Hz approximately 5–7 s after the muscle fasciculations.

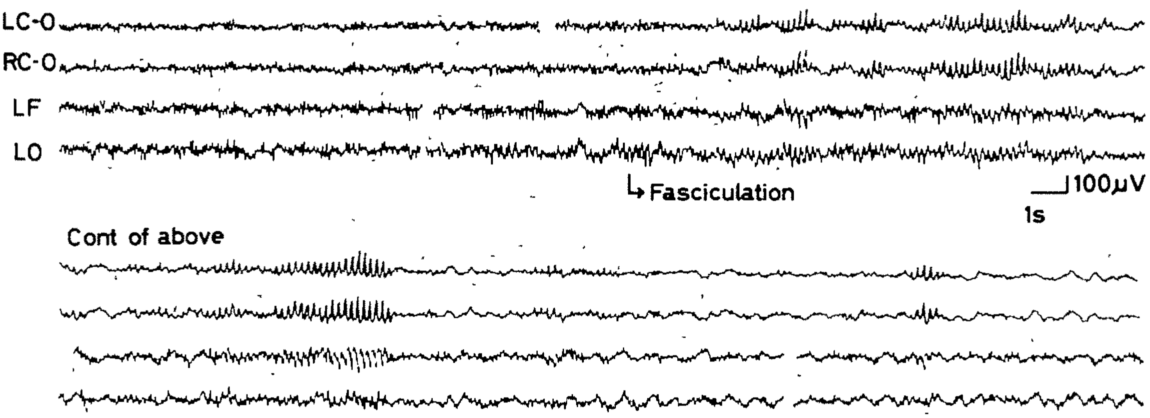

FIG. 4. Theta wave type of e.e.g. activity induced by suxamethonium 1 mg kg^{-1} i.v. in a patient aged 3 yr (patient no. 29). Several seconds after the appearance of muscle fasciculations the e.e.g. is replaced by HVS of theta band activity. The HVS activity is followed by LVF activity at one-third of the lower trace.

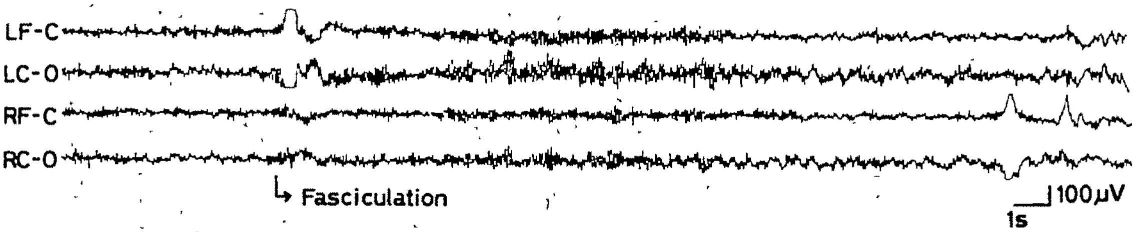

FIG. 5. Alpha wave type of e.e.g. activity induced by suxamethonium 1 mg kg^{-1} i.v. in a patient aged 1 yr 7 months (patient no 21). One to two seconds after the appearance of muscle fasciculations, a sudden increase occurs in e.e.g. voltage. This pattern is similar to barbiturate bursts.

TABLE II. *Classification of e.e.g. activity pattern*

Suxa-methonium	Skin incision	Patient no.	Total
No response	No response	1, 2, 3, 4, 14, 27, 32, 48, 52	9
LVF	LVF	6, 43, 46, 49, 50, 51, 56, 58, 59, 61, 62	11
LVF	No response	37, 41	2
LVF	Artefact	31, 53, 54, 60	4
LVF	HVS	35	1
HVS	HVS	11, 15, 16, 17, 19, 21, 22, 24, 25, 26, 28, 30, 34, 36, 39, 40 42, 45	18
HVS	No response	13, 20, 38, 44	4
No response	HVS	10, 12	2
HVS	Artefact	29, 33	2
Artefact	HVS	9, 18, 23	3

The e.e.g. of four patients aged less than 60 days consisted of a mixture of irregular delta, theta and alpha waves which were different from those of older patients who had waves of 10–12 Hz (Inamoto et al., 1964), and showed no change with either stimulation (table I).

The e.e.g. activities were accompanied by increase in heart rate of 29.9 ±3.9% (mean ± SEM; $P < 0.001$) and increase in systolic arterial pressure of 13.2 ±3% (mean ± SEM; $P < 0.001$) of control following suxamethonium. Heart rate was increased by 26.9 ±3.1% (mean ± SEM; $P < 0.001$) and systolic arterial pressure by 14.2 ±2.7% (mean ± SEM; $P < 0.001$) following skin incision.

TABLE III. *E.e g. patterns of activity in patients aged less than 8 yr*

	LVF	HVS	Total
Suxamethonium	7	24	31
Skin incision	3	23	26

The difference between the effects of suxamethonium and skin incision was not statistically significant. The pupils were dilated by the stimuli. In some patients, these autonomic responses were evident even in the absence of apparent e.e.g. responses.

DISCUSSION

This study confirmed certain aspects of our previous work. First, stimuli such as skin incision and administration of suxamethonium i.v. can induce activation of e.e.g. during light halothane anaesthesia in man (Mori, Iwabuchi and Fujita, 1973). Second, it was demonstrated previously that the e.e.g. of infants aged less than 60 days did not change under halothane anaesthesia and showed a different pattern from that of adults (Inamoto et al., 1964). In this study the neonatal pattern of e.e.g found under anaesthesia did not alter after stimulation. Third, although the background e.e.g. of infants becomes similar to that of adults at the age of approximately 60 days (Inamoto et al., 1964), the pattern of e.e.g. activation can be different in children: the e.e.g. response is represented by HVS in some infants and children, but always by LVF in adults (Mori, Iwabuchi and Fujita, 1973).

Two possible mechanisms can be considered in the production of e.e.g. responses following i.v. administration of suxamethonium. One is the increase in muscle proprioceptive afferent activity and the other is pain secondary to muscle cell injury. Suxamethonium administered i.v. induces sustained contraction of intrafusal muscle fibres (Smith and Eldrid, 1961), while it induces only asynchronous contractions of extrafusal muscle fibres. Thus, there is a marked increase in the activity of muscle afferents (Granit, Skogland and Thesleff, 1953; Rack and Westbury, 1966). Hodes (1962) demonstrated e.e.g. synchronization following gallamine i.v. and considered this to be caused by reduced proprioceptive discharge. Motokizawa and Fujimori (1964) reported desynchronization of e.e.g. following suxamethonium i.v. and ascribed this to the increase in muscle afferent discharge. Hodes (1962) attributed appreciation of the role of muscle proprioception for the regulation of levels of vigilance to Kleitman (1939) who reported that normal human subjects, deprived of sleep for long periods, could remain vigilant as long as they walked around or stood up, while they fell asleep when a significant number of kinesthetic influences were abolished, as when the subjects sat or lay down. Pompeiano and Swett (1962, 1963) and Giaquinto, Pompeiano and Swett (1963) studied the effects of stimulation of muscle afferents on the cat cortical e.e.g. and found that high frequency stimulation of group II afferents of the deep radial nerve induced strong behavioural and e.e.g. arousal response, while that of group II afferents from the hamstring nerve provoked only weak arousal response. They demonstrated that the stimulation of group I afferents had no effect on e.e.g. They suggested that a proportionately larger number of group II afferent fibres other than stretch afferent were present in the radial nerve, which may innervate pain receptors as reported by McIntyre (1962a, b). Although there is no direct morphological evidence, there are reports suggesting muscle fibre injury induced by i.v. administration of suxamethonium. Tamisto and Airaksinen (1966) reported significant increase of CPK concentrations in human blood; Ryan, Kagen and Hyman (1971) reported release of myoglobin into the blood in approximately 20% of children, and Rack and Westbury (1966) reported irreversible change in muscle afferent activity in cats which suggested damage to intrafusal muscle fibres. Thus, pain in muscles and related structures may be part of the mechanism of induction of e.e.g. responses by suxamethonium.

Prince and Shanzer (1966) reported two types of e.e.g. response to identical reticular stimulation during pentobarbitone anaesthesia in cats: LVF response following small doses (3–6 mg kg^{-1}) and HVS response following larger doses (12–25 mg kg^{-1}). Kaada and others (1967) also reported these two types of e.e.g. activation using adult cats anaesthetized with a pentobarbitone–chloralose mixture. However, they emphasized individual differences in the responses: HVS response was predominant in about one-third of animals, LVF in another third, and LVF and HVS were about equally elicited but at different times (possibly different depth of anaesthesia) in the remaining one-third. In our study, HVS was induced in 77% by suxamethonium and in 88% by skin incision in patients aged less than 8 yr, but never in older patients.

We found various e.e.g. types of HVS responses in man. A review of the figures of Kaada and others (1967) revealed similar variations: the delta wave type in their figure 2, the theta wave type in figures

1 and 4 and the alpha wave type in figure 5. In our study, different types of HVS responses were induced in six of 18 patients in whom both forms of stimulation induced HVS responses. There was one patient in our study in whom suxamethonium induced LVF response and skin incision induced HVS response. In the study of Kaada and others (1967), LVF and HVS were equally elicited at different times in one-third of the cats. All these responses suggest that the presence or absence of HVS waves in e.e.g. activation is not rigid and that not only the individual differences and age, but also the depth of anaesthesia may have some role as proposed by Prince and Shanzer (1966). However, since our patients were awaiting surgery and we could not repeat the studies at different depths of anaesthesia, this factor could not be evaluated.

A similar HVS e.e.g. has been described in children during natural sleep when there is some excitatory component, such as following arousal stimulation, the transition from wakefulness to sleep and the paradoxical phase of sleep. During these phases of sleep, more than half the infants and children more than 2 months of age have been reported to produce rhythmic sinusoidal HVS waves of delta to theta range activity, which have been termed "hypersynchrony" for transition from wakefulness to sleep, and "post-arousal hypersynchrony" for the response to stimulation (Kellaway and Fox, 1952). The relationship between the HVS response during anaesthesia and the sleep "hypersynchrony" has not been studied.

Both HVS and LVF responses are probably related to the activation of the central nervous system since it has been confirmed that these e.e.g. responses were accompanied by lightening of anaesthesia (Prince and Shanzer, 1966; Kaada et al., 1967; Bimar and Bellville, 1977).

The basis of the individual differences and the effects of different depth of anaesthesia on the e.e.g. pattern of activation require further clarification.

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ACTIVATION DE L'E.E.G. PENDANT UNE ANESTHESIE A L'HALOTHANE CHEZ L'HOMME

RESUME

Les effets sur l'e.e.g de l'administration intraveineuse de suxaméthonium et de la stimulation nocive induite par l'incision de la peau, ont été étudiés, chez l'homme, pendant une anesthésie à l'halothane Ces stimulants ont induit une activation de l'e.e.g. qui a été représentée soit par des ondes rapides à basse tension, soit par des ondes lentes à haute tension La réaction représentée par des ondes lentes à haute tension a été la réaction prédominante chez les bébés et les enfants âgés de moins de 8 ans. Le suxaméthonium a provoqué la réaction par ondes lentes à haute tension dans 77% des cas; l'incision de la peau dans 88% des cas. L'e.e.g. de quatre bébés âgés de moins de 60 jours n'a accusé d'activation avec aucun des deux stimulants. Les deux types d'activation de l'e.e g. ont été associés à une augmentation de la fréquence cardiaque, à une augmentation de la pression artérielle et à une dilatation des pupilles. Les mécanismes qui sont probablement en cause dans la production de l'activation de l'e e.g. par suite de l'administration intraveineuse de suxaméthonium font l'objet de discussions.

E.E.G.-AKTIVIERUNG WÄHREND HALOTHANNARKOSE BEIM MENSCHEN

ZUSAMMENFASSUNG

Die Auswirkungen einer intravenösen Verabreichung von Suxamethonium, und die schädliche Stimulierung des e e g. durch Hauteinschnitte wurden beim Menschen unter Halothannarkose untersucht. Diese Stimuli bewirkten eine Aktivierung des e.e.g., die sich durch schnelle Niederspannungswellen oder durch langsame Hochspannungswellen manifestierte. Die Reaktion von schnellen Niederspannungswellen wurde bei erwachsenen Patienten beobachtet, wahrend die andere Reaktion vor allem bei Kleinkindern und Kindern unter 8 Jahren auftrat. Suxamethonium rief Reaktion von langsamen Hochspannungswellen in 77% aller Falle hervor; durch Hauteinschnitte wurde die Reaktion in 88% hervorgerufen. Das e.e.g. bei 4 Kindern unter 60 Tagen zeigte keinerlei Aktivierung. Beide Arten der Aktivierung erfolgten zusammen mit Erhöhung von Herztatigkeit, arteriellem Druck und Pupellenerweiterung. Die diese e.e.g.-Aktivierung auslosenden Mechanismen nach Suxamethonium-Verabreichung werden diskutiert.

ACTIVACION DEL ELECTROENCEFALOGRAMA EN EL HOMBRE DURANTE LA ANESTESIA CON HALOTANO

SUMARIO

Durante la anestesia por halotano en el hombre, se estudiaron en el electroencefalograma los efectos de la administración intravenosa de suxametoniom y de la estimulación nociva producida por incisión en la piel. Estos estímulos indujeron la activación del electroencefalograma, el cual se representó mediante ondas rápidas de bajo voltaje o mediante ondas lentas de alto voltaje. La respuesta de ondas rápidas de bajo voltaje se observó en pacientes adultos mientras que la de ondas lentas de alto voltaje fue la respuesta predominante en niños de edades inferiores a 8 años. El suxametoniom indujo la respuesta de ondas lentas de alto voltaje en el 77% de los casos y la incisión en la piel en el 88% de estos Los electroencefalogramas de 4 niños con edades inferiores a 60 días no mostró tal activación bajo ninguno de los estimulos. Ambos tipos de activación del electroencefalograma vinieron asociadas con un incremento del ritmo cardiaco, un incremento de la presión arterial y una dilatación de las pupilas. Se discuten los posibles mecanismos comprometidos en la producción de la activación del electroencefalograma causada por la administración intravenosa de suxametoniom.

Br. J. Anaesth. (1981), 53, 73

MEASUREMENT OF METABOLIC GAS EXCHANGE DURING ANAESTHESIA

A method using mass spectrometry

C. P. H. HENEGHAN, C. E. GILLBE AND M. A. BRANTHWAITE

SUMMARY

A method is described for measuring metabolic gas exchange during general anaesthesia using a respiratory mass spectrometer, a mixing box and two inert tracer gases. Measurement of inspired and expired minute volume is possible to within 2%, oxygen consumption, carbon dioxide output and respiratory quotient can be measured to within 10%.

Metabolic gas exchange is measured conventionally by collection and analysis of expired gases. The composition of the expirate can be analysed in a number of ways, but anaesthetic gases interfere with several instruments, including the mass spectrometer. The calculations also require knowledge of the volume of inspired gas and this is usually derived by assuming that a steady state exists, and that the nitrogen uptake and output of an air-breathing subject are equal. This assumption cannot be used during general anaesthesia because, even if oxygen uptake and carbon dioxide excretion are stable, exchange of inert gases such as nitrous oxide and nitrogen continues in small quantities for many hours.

Davis and Spence (1979) have described a modification to a respiratory mass spectrometer (Centronic MGA 200) which allows the analysis of respiratory gases in the presence of anaesthetic gases and vapours. This system is available commercially, and an evaluation of its performance when installed centrally in a three-room operating theatre suite has been reported recently (Gillbe, Heneghan and Branthwaite, 1981). Unobtrusive methods for measuring metabolic gas exchange by means of mass spectrometry have been described by Davies and Denison (1979) and by Abbott and others (1980), the first of these groups using a mixing box (also available commercially from T. C. Centronic Ltd, Croydon, Surrey) and tracer gas to calculate expired minute volume during procedures such as cardiac catheterization. Their methods can be extended to the measurement of metabolic gas exchange during the unsteady conditions of general anaesthesia by supplying a second inert tracer gas to the inspired mixture and recording its concentration in both inspired and expired gas; details of the technique are reported here.

METHODS

The circuit is illustrated diagrammatically in figure 1. Pure argon was added to the fresh gas flow to the ventilator so that the inspired concentration was 2–5%. The inspired concentrations of argon and oxygen, and the end-tidal concentrations of carbon dioxide and nitrogen were measured in gas

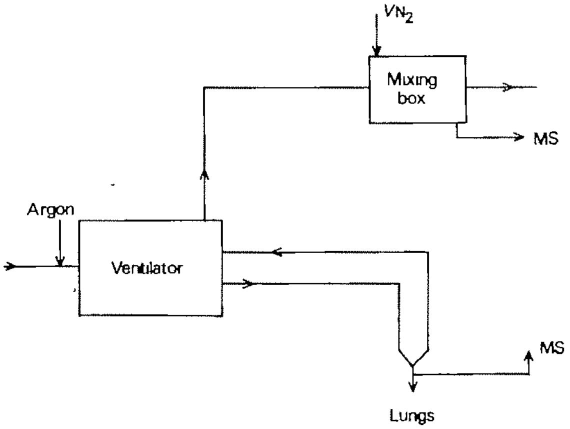

FIG. 1. Circuit used for the determination of metabolic gas exchange during anaesthesia. $\dot{V}N_2$ = known supply of nitrogen to mixing box; MS = mass spectrometer.

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sampled from the endotracheal tube connector. The expired gas was delivered to a mixing box which was situated beyond the expiratory valve of the ventilator. A low flow of nitrogen (200–500 ml min^{-1}) was added to the inlet of the mixing box and the concentrations of oxygen, carbon dioxide, argon and nitrogen in the mixture were measured by sampling from the outlet. The volume flow of nitrogen was measured by timing water displacement from an accurately calibrated 100-ml syringe.

All gas concentrations were measured using the sample delivery system, mass spectrometer and calibration procedure described previously (Gillbe, Heneghan and Branthwaite, 1981). The output from the mass spectrometer was supplied to a four-channel Linzeis recorder, which has a zero-offset on two channels so that small changes can be detected against a larger background signal.

The calculations required to complete the analysis and derive inspired and expired minute volume, oxygen uptake, carbon dioxide output and respiratory quotient are given below. A programmable calculator has been used to complete these stages quickly.

Mixing is considered to occur in two stages: first, mixing of expired gas and second, dilution and mixing of this expirate with a known flow of nitrogen.

The following symbols were used:

FI_{O_2}, FI_{Ar} = fractional inspired concentrations of oxygen and argon;

$F\bar{E}_{O_2}$, $F\bar{E}_{CO_2}$, $F\bar{E}_{N_2}$ = fractional concentrations in mixed expirate of oxygen, carbon dioxide and nitrogen;

FE'_{CO_2}, FE'_{N_2} = fractional end-tidal concentrations of carbon dioxide and nitrogen;

Fm_{O_2}, Fm_{CO_2}, Fm_{Ar}, Fm_{N_2} = fractional concentrations at the exit from the mixing box of oxygen, carbon dioxide, argon and nitrogen;

$\dot{V}_{N_2}$ = flow rate of nitrogen (litre min^{-1});

$\dot{V}_E$, $\dot{V}_I$ = expired and inspired minute volumes (litre min^{-1});

$\dot{V}_{O_2}$, $\dot{V}_{CO_2}$, RQ = oxygen consumption, carbon dioxide output and respiratory quotient.

All fractional gas concentrations were measured dry. $\dot{V}_{N_2}$, $\dot{V}_I$ and $\dot{V}_E$ were expressed at a.t.p.d. during the calculations and, at their conclusion, $\dot{V}_I$ and $\dot{V}_E$ were converted to b.t.p.s., and $\dot{V}_{O_2}$ and $\dot{V}_{CO_2}$ to s.t.p.d. for conventional presentation.

For carbon dioxide:

$$(\dot{V}_E + \dot{V}_{N_2}) \times Fm_{CO_2} = \dot{V}_E \times F\bar{E}_{CO_2} \qquad (1)$$

For nitrogen:

$$(\dot{V}_E + \dot{V}_{N_2}) \times Fm_{N_2} = (\dot{V}_E \times F\bar{E}_{N_2}) + \dot{V}_{N_2} \qquad (2)$$

Rearranging, and dividing (2) by (1):

$$\frac{Fm_{N_2}}{Fm_{CO_2}} - \frac{\dot{V}_{N_2}}{(\dot{V}_E + \dot{V}_{N_2}) \times Fm_{CO_2}} = \frac{F\bar{E}_{N_2}}{F\bar{E}_{CO_2}} \qquad (3)$$

But

$$\frac{F\bar{E}_{N_2}}{F\bar{E}_{CO_2}} = \frac{FE'_{N_2}}{FE'_{CO_2}}$$

Let

$$\frac{FE'_{N_2}}{FE'_{CO_2}} = \alpha$$

Substituting in (3) and rearranging:

$$\alpha Fm_{CO_2}(\dot{V}_E + \dot{V}_{N_2}) = Fm_{N_2}(\dot{V}_E + \dot{V}_{N_2}) - \dot{V}_{N_2}$$

Solving for $\dot{V}_E$:

$$\dot{V}_E = \frac{\dot{V}_{N_2}(1 - Fm_{N_2} + \alpha Fm_{CO_2})}{Fm_{N_2} - \alpha Fm_{CO_2}} \qquad (4)$$

$\dot{V}_I$ is derived from:

$$\dot{V}_I \times FI_{Ar} = (\dot{V}_E + \dot{V}_{N_2}) \times Fm_{Ar} \qquad (5)$$

Using values for $\dot{V}_E$ and $\dot{V}_I$ derived in (4) and (5)

$$\dot{V}_{CO_2} = (\dot{V}_E + \dot{V}_{N_2})Fm_{CO_2} - (\dot{V}_I \times FI_{CO_2})$$

$$\dot{V}_{O_2} = (FI_{O_2} \times \dot{V}_I) - (\dot{V}_E + \dot{V}_{N_2})Fm_{O_2}$$

$$RQ = \frac{\dot{V}_{CO_2}}{\dot{V}_{O_2}}$$

The expression (4) assumes there is neither nitrogen nor carbon dioxide in the inspired gas; if there is, the tracer gas supplied to the mixing box must not be present in the expired gases.

Evaluation. Serial measurements have been made on four patients during cardiac surgery, two patients being studied both before and after cardiopulmonary bypass. Clinical details and the number of measurements made on each subject are given in table I. Anaesthesia was maintained with nitrous oxide 60–70% in oxygen, parenteral analgesics and muscle relaxants. Recordings were made every few minutes for periods of up to 1 h during which both the anaesthetic and the haemodynamic status were considered to be stable.

TABLE I. *Clinical details and number and timing of measurements made on four patients. (a) = measurements made before cardiopulmonary bypass; (b) = measurements made after cardiopulmonary bypass. * Uncuffed endotracheal tube in use; leak around the tube only during inspiration*

	Age (yr)	Weight (kg)	Operation	Measurement period (min)	Number of readings
E.T.	60	64	Insertion of pacemaker	58	13
J.S.	70	69	Aortic valve replacement; pre-bypass	62	17
P.B.*	4.5	18	Repair of sinus venosus defect	(a) 54 (b) 32	12 9
F.S.	61	91	Triple coronary vein graft	(a) 73 (b) 36	13 16

The mean and standard deviation for each variable were calculated for each patient, and the reproducibility of the method was assessed furthur by expressing each individual value as a percentage of the appropriate mean, and then calculating the standard deviation of all these percentages.

TABLE III. *Standard deviations (%) for all values of five variables, when each value has been expressed as a percentage of the appropriate mean.* n = *80*

$\dot{V}_E$	$\dot{V}_I$	$\dot{V}_{O_2}$	$\dot{V}_{CO_2}$	RQ
1.66	1.62	7.70	6.03	9.86

RESULTS

The mean and standard deviation for five variables are shown for each patient in table II. The reproducibility of the method is given in table III which lists the standard deviations of all values expressed as percentages of their appropriate means. The percentage variation was less than 10% for all variables, and less than 2% for inspired and expired volume.

DISCUSSION

The standard technique for measuring metabolic gas exchange has been modified by using a tracer gas, argon, instead of atmospheric nitrogen to detect the difference between inspired and expired volumes. Argon was chosen because it is inert, safe, cheap, virtually insoluble and easily detected by the mass spectrometer.

Attempts to base all the measurements on the addition of a known flow of argon to the fresh gas supply before delivery to the patient were unsuccessful. Gas loss within the ventilator and alterations in flow rate of the tracer caused by back pressure (120 mm Hg in the Blease–Brompton ventilator) preclude quantitative estimations of volume if the tracer is delivered proximal to the ventilator. Inadequate mixing before delivery to the patient invalidates the method if the tracer is supplied on the inspiratory limb of the ventilator

TABLE II. *Mean and standard deviations for five variables determined at the times listed in table I. (a) = measurements made before cardiopulmonary bypass; (b) = measurement made after cardiopulmonary bypass*

Subject	$\dot{V}_E$ (litre min^{-1} b.t.p.s.) (mean ± SD)	$\dot{V}_I$ (litre min^{-1} b.t.p.s.) (mean ± SD)	$\dot{V}_{O_2}$ (ml min^{-1} s.t.p.d.) (mean ± SD)	$\dot{V}_{CO_2}$ (ml min^{-1} s.t.p.d.) (mean ± SD	RQ (mean ± SD)
E.T.	8.35 ± 0.17	8.52 ± 0.18	159 ± 17	126 ± 9	0.79 ± 0.10
J.S.	6.68 ± 0.08	6.84 ± 0.07	168 ± 17	133 ± 6	0.79 ± 0.09
P.B. (a)	5.51 ± 0.03	5.59 ± 0.03	131 ± 5	90 ± 2	0.69 ± 0.03
(b)	5.14 ± 0.03	5.23 ± 0.02	125 ± 6	87 ± 3	0.70 ± 0.03
F.S. (a)	9.77 ± 0.20	10.00 ± 0.23	245 ± 21	187 ± 23	0.76 ± 0.11
(b)	11.39 ± 0.11	11.63 ± 0.09	236 ± 15	174 ± 9	0.74 ± 0.07

circuit. For these reasons, a second tracer was used to quantitate gas flow from the patient through the mixing box and the first tracer was used solely to determine the ratio of inspired to expired volume.

Nitrogen was chosen as the second tracer gas because it is cheap, easy to obtain, and easy to measure in the presence of the other gases (Gillbe, Heneghan and Branthwaite, 1981). It is virtually always present in low concentration in the patient's expirate but, because expired carbon dioxide is diluted in the mixing box to the same extent, the ratio of the end-tidal concentration of nitrogen to that of carbon dioxide can be used to determine the contribution which the patient's expired nitrogen makes to the concentration recorded at the exit from the mixing box. This contribution is trivial except at the very beginning of an anaesthetic, when alveolar nitrogen is being washed out and replaced with nitrous oxide, and is considerably less than 0.5% within 15–20 min. The degree of dilution of carbon dioxide and nitrogen is different if one but not the other is present in the inspired mixture, because the gas in the mixing box includes the compression volume of the ventilator circuit. In these circumstances, the tracer supplied to the mixing box must not be present in the expired gas.

The variability determined in this study may include changes occurring with time but, even so, the figure was less than 10% for all variables. The technique can be used in any circuit where the total expirate can be collected and, although satisfactory measurements are more difficult to make during paediatric anaesthesia because of gas leaks around the endotracheal tube, the method can be used provided the leak only occurs during inspiration and all the expired gas reaches the mixing box.

A comparison with other methods for measuring metabolic gas exchange has not been undertaken. The mixing box technique was validated by Davies and Denison (1979), who compared the values obtained using this method with those derived by conventional collection and analysis of expired air at rest, on exercise, and during i.v. anaesthesia and controlled ventilation with air. The system reported here for measuring expired minute volume is identical and the method has only been elaborated by incorporating a second tracer gas. This means that the inspired volume can be calculated too, even though other inert gases (nitrogen and nitrous oxide) are not in equilibrium.

ACKNOWLEDGEMENTS

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MESURE DE L'ECHANGE EN GAZ METABOLIQUE PENDANT L'ANESTHESIE

Methode utilisant la spectrométrie de masse

RESUME

On décrit dans cet article une méthode permettant de mesurer l'échange en gaz métabolique pendant l'anesthésie générale, à l'aide d'un spectromètre de masse respiratoire, d'une boîte de mélange et de deux gaz inerts marqueurs. On peut mesurer le volume courant inspiré et expiré jusqu'à une précision d'environ 2%; la consommation d'oxygène, le dégagement d'acide carbonique et le quotient respiratoire pouvant être mesurés dans les limites de 10%.

MESSUNG DES METABOLISCHEN GASAUSTAUSCHES UNTER ANÄSTHESIE

Eine Methode unter Verwendung von Massenspektrometrie

ZUSAMMENFASSUNG

Beschrieben wird eine Methode zur Messung des metabolischen Gasaustausches wahrend allgemeiner Narkose mittels eines respiratorischen Massenspektrometers, eines Mischbehalters und zweier inaktiver Tracer-Gase. Die Messung des eingeatmeten und ausgeatmeten Minutenvolumens ist mit einer Genauigkeit von 2% moglich; Sauerstoffverbrauch, Kohlendioxydabgabe und Atmungsquotient konnen innerhalb von 10% gemessen werden.

MEDICIÓN DEL INTERCAMBIO DE GAS METABÓLICO DURANTE LA ANESTESIA

Un método basado en el uso de espectrometría de masas

SUMARIO

Se describe un método para medir el intercambio de gas metabólico durante la anestesia general, usando un espectrómetro de masas de carácter respiratorio, un recipiente de mezclas y dos indicadores de gases inertes Es posible efectuar la medición de pequeños volúmenes de aspiración y de espiración con una tolerancia del 2%; el consumo de oxigeno, la producción de dióxido de carbono y el cociente respiratorio pueden medirse con una tolerancia del 10%

Br. J. Anaesth. (1981), 53, 77

THE CONCEPT OF DEADSPACE WITH SPECIAL REFERENCE TO THE SINGLE BREATH TEST FOR CARBON DIOXIDE

R. FLETCHER, B. JONSON, G. CUMMING AND J. BREW

SUMMARY

We present a review and a theoretical analysis of factors determining airway deadspace ($V\mathrm{D}^{\mathrm{aw}}$) and alveolar deadspace ($V\mathrm{D}^{\mathrm{alv}}$), the two constituents of physiological deadspace ($V\mathrm{D}^{\mathrm{phys}}$). $V\mathrm{D}^{\mathrm{aw}}$ is the volume of gas between the lips and the alveolar/fresh gas interface, the location of which is determined by inspiratory flow pattern and airway geometry. $V\mathrm{D}^{\mathrm{alv}}$ can be caused by incomplete alveolar gas mixing and associated $\dot{V}/\dot{Q}$ mismatching within the terminal respiratory units, temporal $\dot{V}/\dot{Q}$ mismatching within units, spatial $\dot{V}/\dot{Q}$ mismatching between units, and venous admixture. Most causes of $V\mathrm{D}^{\mathrm{phys}}$ are influenced by inspiratory flow pattern and the time available for gas diffusion and distribution. Analysis can be made from the single breath test for carbon dioxide (SBT–$\mathrm{CO_2}$) which is the plot of fraction of carbon dioxide in expired gas against expired volume. The common causes of $V\mathrm{D}^{\mathrm{alv}}$ are associated with a sloping SBT-$\mathrm{CO_2}$ phase III. Combination of SBT-$\mathrm{CO_2}$ with $Pa_{\mathrm{CO_2}}$ yields $V\mathrm{D}^{\mathrm{phys}}$ and $V\mathrm{D}^{\mathrm{alv}}$. A sloping phase III with a negative arterial-end-tidal $P\mathrm{CO_2}$ gradient implies compensation by perfusion for early emptying, overventilated alveoli.

The respiratory deadspace ($V\mathrm{D}$) was originally defined by Bohr (1891):

$$\frac{V\mathrm{D}}{V\mathrm{T}} = 1 - \frac{F\bar{\mathrm{E}}_{\mathrm{CO_2}}}{F\mathrm{A}_{\mathrm{CO_2}}} \tag{1}$$

where

$V\mathrm{T}$ = tidal volume;

$F\bar{\mathrm{E}}_{\mathrm{CO_2}}$ = fraction of carbon dioxide in mixed expired gas;

$F\mathrm{A}_{\mathrm{CO_2}}$ = fraction of carbon dioxide in alveolar gas. ($P\mathrm{CO_2}$ may be used instead of fraction.)

$F\bar{\mathrm{E}}_{\mathrm{CO_2}}/F\mathrm{A}_{\mathrm{CO_2}}$ expresses the extent to which expired gas contains alveolar gas. Hence $V\mathrm{D}/V\mathrm{T}$ defines in some way the part of tidal volume not representative of alveolar gas. For lungs with a non-homogenous $F\mathrm{A}_{\mathrm{CO_2}}$, the definition and sampling of alveolar gas proved to be a source of disagreement which was never satisfactorily resolved, for example the debate between the Oxford and Copenhagen schools reviewed by Bannister, Cunningham and Douglas (1954).

Bohr's equation was later modified by Enghoff (1938) who used $Pa_{\mathrm{CO_2}}$, the partial pressure of carbon dioxide in arterial blood, as a measure of alveolar $P\mathrm{CO_2}$. If the blood is in diffusion equilibrium with alveolar gas, then:

$$\frac{V\mathrm{D}^{\mathrm{phys}}}{V\mathrm{T}} = 1 - \frac{P\bar{\mathrm{E}}_{\mathrm{CO_2}}}{Pa_{\mathrm{CO_2}}} \tag{2}$$

where $V\mathrm{D}^{\mathrm{phys}}$ = physiological deadspace.

Blood is now regarded as "a physiological integrator of the $\mathrm{CO_2}$ pressures existing in all parts of the lung" (Riley et al., 1946). This approach has considerable practical advantages. However, it is important to realize that venous admixture contributes to $V\mathrm{D}^{\mathrm{phys}}$ by increasing $Pa_{\mathrm{CO_2}}$ (equation (2)) and that this contribution does not represent ventilation of any space.

Physiological deadspace can be divided into two or more compartments. Anatomical, series (Folkow and Pappenheimer, 1955) or airway deadspace ($V\mathrm{D}^{\mathrm{aw}}$) is the deadspace created by the convective airways to the point where mixing with alveolar gas occurs. A similar deadspace may be created by apparatus such as mouthpieces etc., connected to the airway.

A second deadspace compartment is the intrapulmonary, parallel (Folkow and Pappenheimer, 1955) or alveolar deadspace ($V\mathrm{D}^{\mathrm{alv}}$) (Severinghaus and Stupfel, 1957).

Airway deadspace

The airway deadspace extends from the lips to the

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interface between inspired and alveolar gas. The nature of this interface has been described by Cumming (1978). Convection can be expressed in terms of a linear velocity of inspired gas, the velocity decreasing continuously as it flows through the airways as a consequence of increasing total airway cross section (fig. 1). This fresh gas creates a concentration gradient which causes diffusive mixing. The diffusion may also be expressed as the velocity of alveolar gas in the opposite direction. The position of the interface between fresh and alveolar gas is determined by the movements of the two gases. During early inspiration, the interface moves rapidly towards the alveoli. If inspiratory flow is constant, it may reach a stationary position, probably in the region of the respiratory bronchioles. The exact position is determined by airway total cross sectional area and geometry, inspiratory flow and the diffusion coefficient of the gas. At the start of expiration, convection rapidly moves the interface into airway segments with a small cross sectional area, where diffusion is unimportant, and then to the airway opening. $V\mathrm{D}^{\mathrm{aw}}$ is the volume of gas expelled when the interface is brought to the lips.

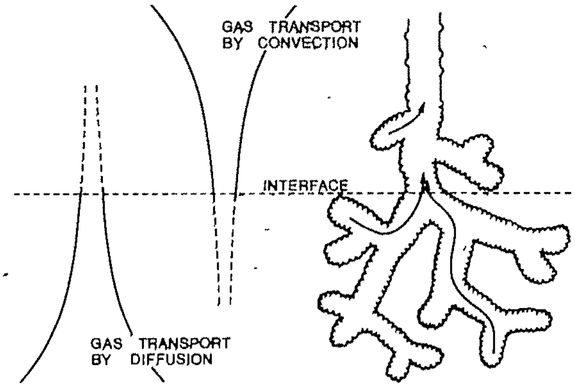

FIG. 1. Factors determining the location of the interface between inspired and alveolar gas. Apart from the diffusion coefficient of the gas in question, these are the linear velocity of the inspired gas (convection) and the velocity of alveolar gas, moving by diffusion, in the opposite direction.

Because functional factors such as inspiratory and early expiratory flow and flow pattern influence the position of the interface, $V\mathrm{D}^{\mathrm{aw}}$ cannot be defined in anatomical terms. It is a functional definition of the volume of the airway in which movement of gases occurs principally by convection. The best descriptive term would be convective airway deadspace.

Alveolar deadspace

Alveolar deadspace is defined by:

$$V\mathrm{D}^{\mathrm{alv}} = V\mathrm{D}^{\mathrm{phys}} - V\mathrm{D}^{\mathrm{aw}} \qquad (3)$$

It includes deadspace from all causes distal to the gas interface. These are ventilation/perfusion ($\dot{V}/\dot{Q}$) mismatching within the terminal respiratory units; $\dot{V}/\dot{Q}$ mismatching between units; the apparent deadspace caused by venous admixture or right to left shunt; and temporal deadspace (table I).

TABLE I. *Causes of alveolar deadspace*

Type of deadspace	Location	Relationship to time
Alveolar mixing defect	Within units $\dot{V}/\dot{Q}$ mismatching	Dependent upon time available for diffusion mixing in units
Spatial maldistribution	Between units $\dot{V}/\dot{Q}$ mismatching	Dependent on time available for between-units distribution (sequential cause) or Time independent (non-sequential cause)
Temporal	Within units $\dot{V}/\dot{Q}$ mismatching	Dependent on differences between flow–time curves of ventilation and perfusion in the same unit
Venous admixture	Non-ventilated units (pulmonary cause) or Outside units (cardiac cause)	Time independent

Mixing within the terminal respiratory unit is most effective proximally but less so distally, implying a series type of deadspace. For this reason we prefer not to use the term series deadspace synonymously with V_D^{aw}.

Spatial $\dot{V}/\dot{Q}$ mismatching is a cause of parallel deadspace as conceived by Folkow and Pappenheimer (1955) in which well perfused and under-perfused units empty simultaneously in parallel. Whether these units empty synchronously or asynchronously will be shown to be of great importance in the analysis of deadspace.

Alveolar deadspace attributable to temporal mismatching of ventilation and perfusion (Cooper, 1961) implies that maximum ventilation and maximum perfusion do not occur simultaneously. The term alveolar deadspace is the only one which satisfactorily describes this group of deadspaces distal to the interface. It is inappropriate only in the presence of cardiac left-to-right shunts, when the cause lies outside the alveolar region.

The measurement of dead space

The classical method for estimation of V_D^{phys} is collection of expired air over a period of a few minutes during steady state with simultaneous sampling of arterial blood. P_{CO_2} of both samples is then determined and deadspace fraction calculated from equation (2). If V_T is known, the absolute value for V_D is obtained.

The same principle may be applied to a single expiration. Figure 2 represents the plot of expired carbon dioxide fraction ($F_{E'CO_2}$) against expired volume, which is the single breath test for carbon dioxide (SBT-CO_2). The features of the tracing are:

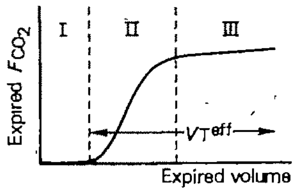

FIG. 2. The three phases of SBT–CO_2. Phase I is the carbon dioxide-free ineffective tidal volume, or absolute deadspace. Phase II represents the transition between airway and alveolar gas. Phases II and III together are the carbon dioxide-containing part of the breath or effective tidal volume. Phase III slopes upwards because low $\dot{V}/\dot{Q}$ alveoli with high $P_{A_{CO_2}}$ content make a relatively larger contribution to late expiration, and alveolar P_{CO_2} increases continually during expiration.

phase I, represents carbon dioxide-free gas from the airway deadspace,

phase II, the S-shaped upswing which represents the transition between airway and alveolar gas,

phase III, the alveolar plateau, representing carbon dioxide-rich gas from the alveoli.

Phase I should not include apparatus deadspace unless specified. Phases II and III together represent the effective part of tidal volume (V_T^{eff}) that contributes to gas exchange.

Fowler (1948) measured *airway deadspace* from the plot of expired nitrogen after a breath of oxygen against expired volume by extrapolating phase III to the left and placing a perpendicular so as to divide phase II into two triangles of equal area (fig. 3). V_D^{aw} is the volume to the left of the perpendicular. Similar values for V_D^{aw} are obtained using SBT-CO_2 (Bartels et al., 1954).

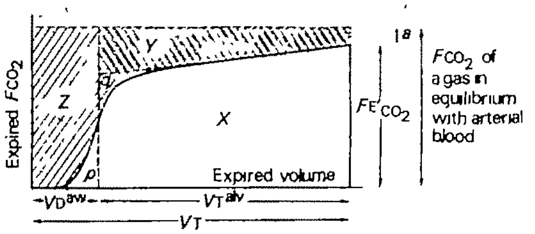

FIG. 3. Physiological deadspace and its subdivisions as illustrated by the single breath test for carbon dioxide modified from Fowler (1948) and Nunn (1977d). Triangles *p* and *q* are of equal area. *a* = end-tidal-arterial F_{CO_2} difference.

An alternative presentation of SBT-CO_2 is that of Langley and others (1975), who plotted the volume of expired carbon dioxide against expired volume (fig. 4). This produces almost a linear tracing which can be extrapolated to the x-axis. V_D^{aw} corresponds well with that determined by Fowler's method.

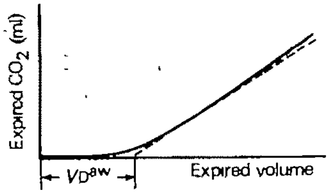

FIG. 4. The method of Langley and others (1975) for estimation of airway deadspace. Expired carbon dioxide volume is plotted against expired volume. The first almost linear part of the tracing is extrapolated back to the x-axis, which is intersected at V_D^{aw}.

Neither method is easy to apply when the transition from phase II to phase III is not clear. The latter part of the transition is influenced by factors distal to the interface such as increase in PA_{CO_2} with time. These are irrelevant to VD^{aw} and must be avoided during its determination. One solution may be to let the point of inflexion in phase II represent the end of VD^{aw}.

Whichever method is used, by definition VD^{aw} represents the volume of gas already expired, plus that remaining between the lips and the interface at the moment early in expiration when the interface leaves the airway segments where diffusion is of importance. Methods involving use of end-tidal carbon dioxide values, as described by Nunn (1977a), are incorrect in concept and produce large errors since a number of factors not related to VD^{aw} affect the late part of expiration (Mundt, Schoedel and Schwarz, 1940; Bouhuys, 1964).

Having determined VD^{aw}, alveolar tidal volume may be estimated from:

$$VT^{alv} = VT - VD^{aw} \tag{4}$$

VT^{alv} can be broken down into two components:

$$VT^{alv} = VD^{alv} + VGE^{alv} \tag{5}$$

VGE^{alv} is the notional part of the tidal volume which, through gas exchange, equilibrates with arterial blood. The conventional term alveolar ventilation ($\dot{V}^{alv}$) is therefore given by the product of VGE^{alv} and ventilatory frequency.

A second addition to SBT-CO_2 may be made: the fraction of carbon dioxide of a gas in equilibrium with arterial blood (Fa_{CO_2}) is represented by the dotted horizontal line in figure 3. The area below the arterial carbon dioxide line can be divided into three parts, *X*, *Y* and *Z*. The advantage of using fractions of carbon dioxide compared with partial pressures is that each area represents a volume of carbon dioxide, real or theoretical. The sum of the areas represents the volume of carbon dioxide that would have been exhaled from a lung without any form of deadspace, $VT \times Fa_{CO_2}$.

Area X = tidal elimination of carbon dioxide (VT_{CO_2}) with the effective part of VT,

Area Y represents wasted ventilation as a result of VD^{alv},

Area Z represents wasted ventilation as a result of VD^{aw}.

These areas can be used to express various deadspace fractions:

$$\frac{VD^{aw}}{VT} = \frac{Z}{X+Y+Z} \tag{6}$$

$$\frac{VD^{alv}}{VT} = \frac{Y}{X+Y+Z} \tag{7}$$

$$\frac{VD^{alv}}{VT^{alv}} = \frac{Y}{X+Y} \tag{8}$$

and

$$\frac{VD^{phys}}{VT} = \frac{Y+Z}{X+Y+Z} = 1 - \frac{X}{X+Y+Z} \tag{9}$$

In clinical work, measurements are often made under practical constraints. Arterial blood cannot always be sampled and analysed. During artificial ventilation, gas compression and apparatus deadspace are not easily separated from VD^{aw}, and phase II may be difficult to distinguish from phase III. To extract information from readily obtained data we suggest a method closely related to Bohr's concept in which end-tidal F_{CO_2} (FE'_{CO_2}) is related to $F\bar{E}_{CO_2}$. Figure 5 represents how VT_{CO_2} (area *X*) can be related to the volume of carbon dioxide hypothetically eliminated by a breath in which the whole effective volume has carbon dioxide fraction equal to FE'_{CO_2} (area ABCDA). The ratio

$$\frac{X}{\text{area ABCDA}} = \frac{VT_{CO_2}}{VT^{eff} \times FE'_{CO_2}} \tag{10}$$

describes the efficiency of the effective volume in eliminating carbon dioxide.

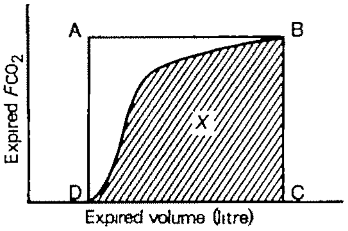

FIG 5 Estimation of efficiency. Area *X*, the volume of carbon dioxide contained in the breath is related to area ABCDA, or the volume of carbon dioxide that would have been eliminated by a theoretical ideal lung with the same effective tidal volume and end-tidal F_{CO_2}. The term is related to Bohr's original deadspace concept.

In studies performed in patients under anaesthesia during intermittent positive pressure ventilation (IPPV) we call this ratio "efficiency".

The factors on the right in equation (10) were obtained from a CO_2 Analyzer 930 (Siemens–Elema). The term (1 – efficiency) is analogous to a deadspace fraction caused by inhomogeneity of expired gas during phases II and III.

We have stated that deadspace is not a rational term for variables calculated from $F\text{E}'_{CO_2}$. To distinguish these from deadspace compartments derived from a unified concept ($V\text{D}^{aw}$ and $V\text{D}^{alv}$) we prefer to use the term efficiency.

Factors affecting $V\text{D}^{aw}$

Nunn (1977b) lists as factors influencing $V\text{D}^{aw}$ the size of the subject, posture, position of neck and jaw, the presence of a tracheostomy or tracheal tube. These, together with changes in airway calibre related to transmural pressure (Hedenstierna and Lundberg, 1975), play a large part in determining the volume of the airway proximal to the interface.

The exact location of the interface in anatomical terms is determined by airway geometry, inspiratory flow, and diffusion coefficient. Whilst convection drives the interface distally, diffusion moves it proximally. Circumstances favourable for diffusion, such as large surface area and increased time, reduce $V\text{D}^{aw}$ by allowing a proximal shift of the interface before it becomes driven distally by convective expiratory movement to smaller surface areas.

A *high initial inspiratory flow* will rapidly move the interface to zones where diffusion is of importance, so increasing time available for diffusion. A *low late inspiratory flow* and, more important an end-inspiratory pause (EIP) will be associated with reduced $V\text{D}^{aw}$. Therefore decelerating inspiratory flow combined with EIP would give the smallest values for $V\text{D}^{aw}$.

The theoretical considerations of effects of transmural pressure and EIP are supported by the studies of Bartels and others (1954), Shephard (1956), Shephard and others (1957), Lyager (1970), Knelson, Howatt and DeMuth (1970), and Fuleihan, Wilson and Pontoppidan (1976). In addition, the studies of Modell and Cheney (1979) and Baker, Colliss and Cowie (1977) although only referring to $V\text{D}^{phys}$, support our predictions of the effects of flow pattern on "residence time" (Modell and Cheney, 1979), or "mean distribution time" (Nordström, Jonson and Olsson, in preparation) of inspired gas.

For a given $V\text{D}^{aw}$, the volume occupied by phase II depends on the spread of transit times (Horsfield and Cumming, 1968). If all the different parts of the interface arrive at the lips simultaneously, phase II would derive its shape primarily from the washout of the airway. Staggered arrival of the parts of the interface will increase the volume occupied by phase II. The spread of transit times for a given lung may be influenced by distribution of the inspired gas with even distribution producing least spread. The non-linearity of the alveolar pressure–volume relationships contributes to this: improved filling of "slow" regions leads to reduction of their compliance and probably resistance. Slower units thus reduce their time constants, and empty more rapidly initially.

Since phase II volume is determined in part by airway washout, it should be least during turbulent flow such as with high expiratory flow at the beginning of passive expiration and greatest during more laminar flow (Nunn, 1977c), as for example during spontaneous breathing at rest. In the latter example, phase I is reduced correspondingly. This may allow some alveolar ventilation at very low tidal volumes (Nunn, 1977c) when the gas volume within the conductive airways may not be fully washed out. The part that is washed out was referred to by Gray, Grodins and Carter (1956) as "dead air", and approximates to $V\text{D}^{aw}$ at large tidal volumes.

However, neither the mode of washout nor spread of transit times can influence $V\text{D}^{aw}$ itself since this is determined entirely by the location of the interface.

Factors affecting alveolar deadspace

Alveolar deadspace as a result of venous admixture

Enghoff's substitution of Pa_{CO_2} in the Bohr equation (equation (2)) implies that venous admixture contributes an apparent deadspace, although Riley and others (1946) pointed out that its effect was usually small enough to be neglected since the mixed venous–arterial carbon dioxide difference is small. Venous admixture may increase at high airway pressure (Landmark et al., 1978) probably by increasing blood flow through non-ventilated lung (Karanek and Shannon, 1975).

Alveolar dead space as a result of incomplete diffusive mixing

Incomplete mixing may be associated with spread of $\dot{V}/\dot{Q}$ ratios within the terminal respiratory units and hence contribute to deadspace (West, 1969). The degree of mixing varies axially along the unit. Because it occurs in a compartment in which diffusion is the principle mode of movement of gas molecules (Gomex, 1965), this form of deadspace is time-dependent. All factors which promote diffusion within units reduce $V_D{}^{alv}$ For example, Fowler (1949) showed that breath-holding reduced the slope of phase III of SBT-N_2. Incomplete mixing is one of the causes of the slope of phase III of SBT-CO_2.

The presence of alveoli along several generations of ducts from the respiratory bronchiole (fig. 1) suggests an additional beneficial mechanism associated with EIP. Although movement of gas from alveolus to duct is mainly caused by diffusion, convection plays an increasing role nearer the respiratory bronchiole as gas from peripherally located alveoli flows past. Gas from proximally located alveoli, required after a short time for diffusion into the convective midstream, may thus be transported by both diffusion and convection. Gas from more peripheral alveoli and ducts takes a longer time for diffusion into the zone of increasing convection. EIP may allow sufficient time for this to occur.

Alveolar deadspace as a result of spatial, between-units, $\dot{V}/\dot{Q}$ mismatching

Spatial ventilation/perfusion mismatching arises from differences between parallel units. Regional variation in ventilation per unit perfusion produces a spectrum of $\dot{V}/\dot{Q}$ ratios and causes alveolar deadspace. Certain causes of this dead space form are also time-dependent, in particular when ventilation is maldistributed because of differences in mechanical time constants between lung compartments. This form of $\dot{V}/\dot{Q}$ mismatching is reduced by factors favouring even ventilation, namely low inspiratory flow rates with prolonged inspiration; decelerating inspiratory flow; and end-inspiratory pause (Jansson and Jonson, 1972). It is reduced by increasing distribution time.

Differences in mechanical properties are associated with sequential or asynchronous emptying of various units. Allied to $\dot{V}/\dot{Q}$ spread, this results in a sloping phase III of SBT-CO_2, which is typical of "sequential" causes of alveolar deadspace. Area Y (fig. 3) is therefore triangular or wedge-shaped.

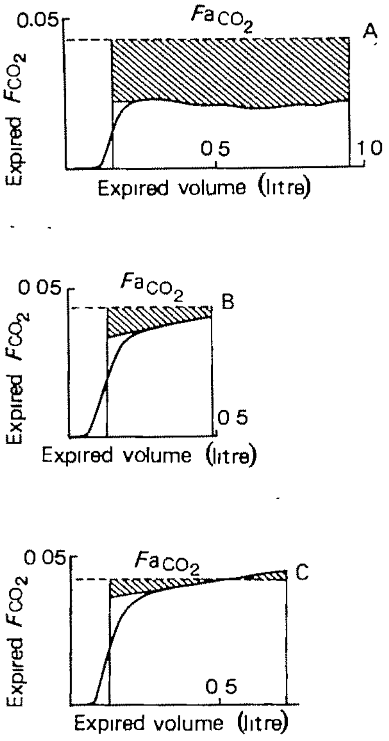

FIG. 6. A: SBT–CO_2 recorded from a patient with carcinoid tumour under anaesthesia and during IPPV. $f = 10$ b.p.m.; $(Fa_{CO_2} - F\bar{E}'_{CO_2})/Fa_{CO_2} = V_D{}^{alv}/V_T{}^{alv} = 0.52$. The horizontal phase III suggests synchronous alveolar emptying where alveolar deadspace is essentially of non-sequential cause. B: SBT–CO_2 recorded under anaesthesia during IPPV. $f = 21$ b.p.m.; $(Pa_{CO_2} - P\bar{E}'_{CO_2}) = 0.3$ kPa; $V_D{}^{alv}/V_T{}^{alv} = 0.15$. C: SBT–$CO_2$ recorded under anaesthesia during IPPV in the same patient as in tracing B. $f = 10$ b.p.m.; $(Pa_{CO_2} - P\bar{E}'_{CO_2}) = -0.2$ kPa; $V_D{}^{alv}/V_T{}^{alv} = 0.06$. Figures B and C illustrate the effect of reducing f and increasing V_T in individuals with alveolar deadspace of mainly sequential cause.

However, spatial $\dot{V}/\dot{Q}$ mismatching may occur in the absence of large differences in mechanical properties. Examples are pulmonary embolism (fig. 6A), the carcinoid syndrome (unpublished observations from this department), pulmonary ligation (Langley et al., 1975) and pulmonary hypotension (Prakash et al., 1978). In this form of $\dot{V}/\dot{Q}$ mismatching, which may be regarded as non-sequential, gas from well- and underperfused lung regions is expired synchronously, as a true "parallel" deadspace (Folkow and Pappenheimer, 1955). This non-sequential form of deadspace is essentially independent of time since, with the exception of some cardiogenic mixing between adjacent segments, there is no temporal mechanism that can improve overall $\dot{V}/\dot{Q}$. Non-sequential deadspace is characterized by an almost horizontal phase III in SBT-CO_2 which does not reach the arterial carbon dioxide value. Area *Y* (fig. 3) has therefore approximately a rectangular shape.

Temporal deadspace

Temporal deadspace occurs within units. The concept was developed by Cooper (1961) and Lewis and Burn (1977) to explain the large values for V_D^{phys} observed during IPPV. Whereas expiration during spontaneous breathing at rest has approximately a square wave form, the flow pattern of passive expiration is approximately exponential (Kavan and Haddy, 1956). This implies that the greater part of gas leaves the alveoli at high flows early in expiration and that the last of the gas leaves at low flows. The pattern of pulmonary blood flow during IPPV is the opposite: flow is maximum towards the end of expiration (Nordström, 1972). There is therefore temporal mismatching of ventilation and perfusion which produces ventilation–perfusion time-dependent alveolar deadspace. Temporal deadspace implies that Pa_{CO_2} varies during the respiratory cycle. The fluctuations and the deadspace will be greatest when FRC is small since the gas remaining at the end of expiration acts as a buffer against large changes in alveolar gas composition.

Anaesthesia with controlled ventilation may thus favour temporal $\dot{V}/\dot{Q}$ mismatching by its effects on expiratory flow pattern, cyclical variations in alveolar perfusion and reduction of FRC.

The alveolar evolution of carbon dioxide

A further factor affecting the shape of SBT-CO_2 recorded at the lips, is the manner in which the alveolar carbon dioxide concentration increases during expiration.

Although it is not possible to record an alveolar carbon dioxide diagram, several analyses have been performed to relate alveolar CO_2 to expired volume. Those of Chilton and Stacey (1952) and DuBois, Britt and Fenn (1952) describe events during spontaneous ventilation. A mathematical model was devised for exponential expiratory flow seen during IPPV in which cycle times, lung volume, tidal volume, and time constants can be varied (see Appendix). Figure 7 shows two typical tracings obtained from the model. The lower one is

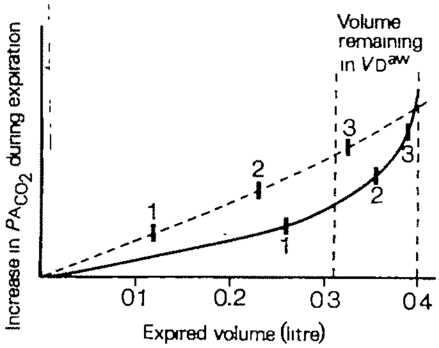

FIG 7. Analysis of alveolar P_{CO_2} during IPPV with exponential expiratory flow pattern. FRC in both cases is 2.5 litre. *Lower tracing:* Alveolar carbon dioxide curve from "fast" alveolus (time constant 0.5 s): time in seconds marked on tracing. Most of the expired gas is exhaled in the 1st second and therefore does so at an almost constant F_{CO_2}. As gas flow is reduced, F_{CO_2} increases steeply, but much of this gas remains in the airway deadspace and the increase is therefore not recorded at the mouth. The *upper tracing* is from a slow alveolus (time constant 2.5 s), where the expiratory flow rate is more constant and therefore the increase in F_{CO_2} is spread more evenly over the tidal volume. The initial rate of increase is steeper than for fast alveoli, and the slope increases gradually as flow rate decreases.

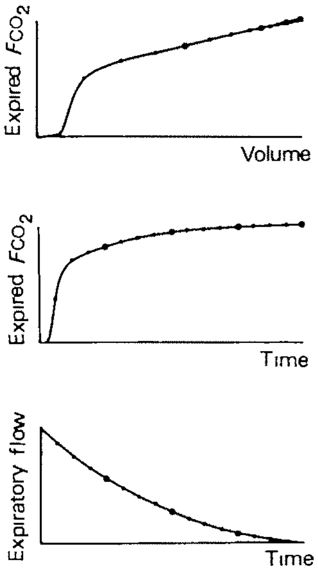

FIG. 8 Comparison of tracings of expired carbon dioxide against volume (upper) and time (middle) during controlled ventilation. The expiratory flow pattern is seen in the lower diagram. Time markings are 0.25 and 1 s (large dots) On the volume plot it can be seen that, late in expiration, expired volumes represent successively longer time periods On the time plot, information concerning the greater part of the expired volume is compressed The last 15% of expired gas occupies half the time available so that phase III has a shallower gradient than on the volume plot.

for an alveolus with small time constants and rapid emptying. The high initial expiratory flow rate implies that most of the gas leaves the alveolus with almost a constant $P\mathrm{CO_2}$. Later, when expired volumes represent longer time periods (fig. 8) the carbon dioxide content of the expired gas increases more steeply producing a "knee" in the tracing of carbon dioxide against expired volume. For "fast" alveoli, the "knee" is always placed far to the right and will be partly concealed within the airway deadspace.

Slower lungs empty at a more even rate. Even from the start the slope is greater as more time is allowed for carbon dioxide to accumulate in the alveoli. The slope increases more gradually as flow rate decreases. Theoretically, slow alveoli should have less temporal deadspace than fast alveoli. If the alveolar carbon dioxide diagram was transmitted unchanged to the lips, slow alveoli would produce a sloping phase III while that from fast alveoli would be almost horizontal.

The relationship between alveolar deadspace and the arterial–end-tidal carbon dioxide difference

Previous investigators of alveolar deadspace have stressed the importance of the arterial to end-tidal $P\mathrm{CO_2}$ or $F\mathrm{CO_2}$ difference, but the relationship between arterial carbon dioxide and the whole of phase III of SBT-$\mathrm{CO_2}$ is of interest in the analysis of $V\mathrm{D}^{\mathrm{alv}}$.

In figure 3 alveolar deadspace is represented by the area between $F\mathrm{a}_{\mathrm{CO_2}}$ and phase III, area Y. This area may have various forms such as almost rectangular, or triangular (or wedge-shaped). Figure 6A shows an example of the former. According to the single breath concept put forward by Comroe (1962), this implies synchronous emptying of lung units, regardless of the range of $\dot{V}/\dot{Q}$ values to be found in the lung. A slight slope of phase III can be attributed mainly to the continued evolution of carbon dioxide gas in the alveoli (West et al., 1957). The flat phase III also implies that there is no important mixing defect in lung units. However, a large number of alveoli are under- or non-perfused, as represented by the large ($F\mathrm{a}_{\mathrm{CO_2}}$ – phase III) difference. Since this difference is almost constant, it is adequately represented by the arterial–end-tidal difference, $(F\mathrm{a}_{\mathrm{CO_2}}-F\mathrm{E}'_{\mathrm{CO_2}})$. The term

$$\frac{(F\mathrm{a}_{\mathrm{CO_2}}-F\mathrm{E}'_{\mathrm{CO_2}})}{F\mathrm{a}_{\mathrm{CO_2}}}$$

modified from Nunn and Hill (1960), was pointed out by them to represent the fraction of gas from non-perfused alveoli. When phase III is horizontal, the term is identical to $Y/(X+Y)$ in figure 3 ($V\mathrm{D}^{\mathrm{alv}}/V\mathrm{T}^{\mathrm{alv}}$). It should not be related to $V\mathrm{D}^{\mathrm{alv}}/V\mathrm{T}$, as was done by Nunn and Hill, because of the irrelevance of $V\mathrm{D}^{\mathrm{aw}}$ to alveolar ventilation.

Another consequence of this form of deadspace is that $(F\mathrm{a}_{\mathrm{CO_2}}-F\mathrm{E}'_{\mathrm{CO_2}})$ is not dependent upon tidal volume in a given individual. It will be shown elsewhere that this non-sequential form is not a common type of alveolar deadspace. It is time-independent since there is no temporal mechanism by which this $\dot{V}/\dot{Q}$ mismatching can be improved. Pulmonary embolism, ligation and hypotension, and the carcinoid syndrome have been named as causes. Massive right–left shunting will also produce a similar effect.

Alveolar deadspace associated with a sloping phase III

The second possibility for the shape of area Y is that created by a sloping phase III which may or may not achieve a value equal to $F\mathrm{a}_{\mathrm{CO_2}}$ (fig. 6B). The slope in phase III may be attributed to the evolution of carbon dioxide gas within the alveoli; sequential (asynchronous) emptying of lung regions with differing $\dot{V}/\dot{Q}$ ratios; and defective alveolar mixing with associated, within units, $\dot{V}/\dot{Q}$ scatter.

In these forms of alveolar deadspace, increasing tidal volume extends the upward progress of phase III. For a given individual, therefore, increasing tidal volume causes a reduction in $(F\mathrm{a}_{\mathrm{CO_2}}-F\mathrm{E}'_{\mathrm{CO_2}})$.

The shape of alveolar deadspace area Y here implies that the $(F\mathrm{a}_{\mathrm{CO_2}}-F\mathrm{E}'_{\mathrm{CO_2}})$ difference no longer represents $V\mathrm{D}^{\mathrm{alv}}$. If, for example, $V\mathrm{T}$ is increased so that $(F\mathrm{a}_{\mathrm{CO_2}}-F\mathrm{E}'_{\mathrm{CO_2}})$ becomes zero, there will still be an area Y and therefore alveolar deadspace. Nunn and Hill's supposition does therefore not apply when phase III has a slope. The probable reason for the opposite conclusion reached by them is that they studied the tracing of expiratory carbon dioxide against time. Figure 8 shows that a steeply sloping phase III on the volume plot can appear to have only a shallow slope on the time plot during IPPV and resembles non-sequential alveolar deadspace.

Nunn and Hill (1960) believed that the scatter in the relationship between $(F\mathrm{a}_{\mathrm{CO_2}}-F\mathrm{E}'_{\mathrm{CO_2}})/F\mathrm{a}_{\mathrm{CO_2}}$ and $V\mathrm{D}^{\mathrm{alv}}/V\mathrm{T}^{\mathrm{alv}}$ was a result of experimental error. The scatter may also be caused by, first, use of $V\mathrm{T}$

instead of $V\text{T}^{\text{alv}}$ as the denominator, and second, between-individual variation in phase III, in particular its slope and relationship to Fa_{CO_2}. This variation can be expressed as follows:

$$\frac{V\text{D}^{\text{alv}}}{V\text{T}^{\text{alv}}} = \frac{Fa_{\text{CO}_2} - F\bar{\text{A}}_{\text{CO}_2}}{Fa_{\text{CO}_2}} \quad \text{(Bohr, 1891)} \qquad (11)$$

where mean alveolar carbon dioxide fraction ($F\bar{\text{A}}_{\text{CO}_2}$) is regarded as the midpoint of phase III(fig. 9). In this figure:

$$F\text{E}'_{\text{CO}_2} = F\bar{\text{A}}_{\text{CO}_2} + \text{slope} \times \frac{V\text{T}^{\text{alv}}}{2} \qquad (12)$$

where "slope" is a gradient with units $\Delta F\text{CO}_2$ litre^{-1} and represents a linear increase of $F\text{CO}_2$ against expired volume. This is an acceptable approximation at least during IPPV and permits a valid discussion of the principles involved.

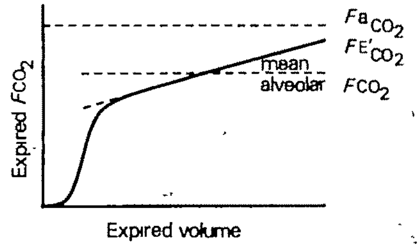

FIG. 9. Illustration of the explanation of the scatter in the regression of $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$ against $(Fa_{\text{CO}_2} - F\text{E}'_{\text{CO}_2})/Fa_{\text{CO}_2}$. Mean alveolar $F\text{CO}_2$ ($F\text{A}_{\text{CO}_2}$) is the midpoint of the (extrapolated) phase III.

From equation (12),

$$F\bar{\text{A}}_{\text{CO}_2} = F\text{E}'_{\text{CO}_2} - \text{slope} \times \frac{V\text{T}^{\text{alv}}}{2}$$

and substituting in equation (11):

$$\frac{V\text{D}^{\text{alv}}}{V\text{T}^{\text{alv}}} = \frac{Fa_{\text{CO}_2} - F\text{E}'_{\text{CO}_2} + \text{slope} \times (V\text{T}^{\text{alv}}/2)}{Fa_{\text{CO}_2}}$$

A scatter of the kind Nunn and Hill observed must be expected to equal

$$\frac{\text{slope} \times (V\text{T}^{\text{alv}}/2)}{Fa_{\text{CO}_2}}$$

Further increase in $V\text{T}$ beyond the point where $(Fa_{\text{CO}_2} - F\text{E}'_{\text{CO}_2})$ is zero, results in a negative value for $(Fa_{\text{CO}_2} - F\text{E}'_{\text{CO}_2})$, a finding we have frequently observed. The appearance of SBT-CO$_2$ is now that of figure 6C. This tracing is from the same patient as figure 6B, but with a larger tidal volume and lower frequency. There are two triangles; the area of the upper one may approach that of the lower. If the lower triangle represents ventilation in excess of that needed to achieve Fa_{CO_2}, the upper triangle may be regarded as representing compensatory perfusion of late emptying compartments in excess of that required to achieve Fa_{CO_2}. It should be remembered that the dotted line in figure 6 represents the spatial and temporal mean Fa_{CO_2}, and that negative $(Fa_{\text{CO}_2} - F\text{E}'_{\text{CO}_2})$ values need not imply carbon dioxide diffusion against a concentration gradient.

The expression $(Fa_{\text{CO}_2} - F\text{E}'_{\text{CO}_2})/Fa_{\text{CO}_2}$ now has a negative value, and increasing tidal volumes causing increasing negativity are associated with reductions in $V\text{D}^{\text{alv}}/V\text{T}^{\text{alv}}$ which tends towards zero as compensation improves.

APPENDIX

This model describes the change of $P\text{A}_{\text{CO}_2}$ with respect to time or expired volume. The analysis follows those of Chilton and Stacey (1952), and Dubois, Britt and Fenn (1952) and the physiological justifications of the assumptions needed are well covered by these authors. The present analysis differs in that the rate of expiration is taken to be reducing exponentially rather than constant.

$P\text{A}_{\text{CO}_2}$ changes because carbon dioxide is transferred from the blood to the alveoli throughout the respiratory cycle. The rate of transfer is not constant since it depends on $P\text{A}_{\text{CO}_2}$ itself; as this increases, the rate of diffusion of carbon dioxide from the venous blood decreases. Further, the rate of change of $P\text{A}_{\text{CO}_2}$ depends on alveolar volume, so that the change of volume with time must also be considered.

Let the volume of blood flowing through the alveolar capillaries during small time interval, δt, be $y\delta t$. The decrease in partial pressure is $P\bar{\text{v}} - p$ where $P\bar{\text{v}}$ is mixed venous $P\text{CO}_2$ and p is $P\text{A}_{\text{CO}_2}$ at time t, diffusion to equilibrium being assumed to be instantaneous. This change manifests itself as an increase in the volume of carbon dioxide in the alveoli. The conversion rate is the physiological dissociation constant, a, and includes the effect of oxygen in the blood. The increase in carbon dioxide volume is thus:

$$\delta C_1 = a(P\bar{\text{v}} - p)\,y\delta t$$

The effect on alveolar volume of RQ, being other than 1, is negligible compared with the expiratory flow. If alveolar volume V changes by δV (which will be negative for expiration) then the corresponding change in volume of carbon dioxide is

$\delta C_2 = p\delta V/\pi$ where π is atmospheric pressure. The total change in carbon dioxide volume is therefore:

$$\delta C = \delta C_1 + \delta C_2 = a(P\bar{\text{v}} - p)\,y\delta t + p\delta V/\pi$$

Converting to partial pressures the change is:

$$\delta p = (p+\delta p)-p = \pi(C+\delta C)/(V+\delta V)-\pi C/V$$
$$= a\pi(P\bar{v}-p)\,y\delta t/V + \text{second order terms}$$

Therefore

$$\frac{\mathrm{d}p}{\mathrm{d}t} = a\pi(P\bar{v}-p)\,y/V \qquad (1)$$

Substituting y and V as functions of time enables the differential equation (1) to represent different expiratory patterns.

In particular, assuming blood flow is constant and expiration rate is negatively exponential then:

$$\frac{\mathrm{d}p}{\mathrm{d}t} = a\pi(P\bar{v}-p)\,y/[V_0-u(1-\mathrm{e}^{-t/\alpha})]$$

and

$$p_t = p_0+(P\bar{v}-p_0)[V_0/\{u+(V_0-u)\mathrm{e}^{t/\alpha}\}]^{\pi a y\alpha/(V_0-u)} \qquad (2)$$

where subscripts of p and V represent time from the start of expiration. End-expiratory lung volume is (V_0-u) and the tidal volume is $u(1-\mathrm{e}^{-T/\alpha})$, where T is the duration of expiration, and u and α are volume and time constants. For realistic values of constants and variables equation (2) is well approximated by the linear form.

$$\hat{p}_t = p_0+(P\bar{v}-p_0)\pi a y t/V_0 \qquad (3)$$

Note that the expiration rate time constant, α, does not appear explicitly This is because the proportionate change in alveolar volume is small and the main determinant of $P\text{A}_{CO_2}$ is time. However, if volume rather than time is used as the independent variable, then α is very important. Substituting for t in equations (2) or (3) gives the appropriate expression. From equation(3):

$$\hat{p}_t = p_0+(P\bar{v}-p_0)\pi a y\frac{\alpha}{V_0}\ln\{u/(u-V_{(t)})\} \qquad (4)$$

where the expired volume at time, $V_{(t)}$, is given by

$$V_{(t)} = u(1-\mathrm{e}^{-t/\alpha})$$

Pa_{CO_2} is the temporal average of p over inspiration and expiration and, since the variation of p is nearly linear with time for both of these (Chilton and Stacey, 1952, Dubois, Britt and Fenn, 1952), then $P\bar{a}_{CO_2} = p_{T/2}$, the value of p halfway through expiration. The volume of gas ($V\bar{a}$) expired at this time, is given by:

$$V\bar{a} = u(1-\mathrm{e}^{-T/2\alpha}) = V_{(T)}/(1+\mathrm{e}^{-T/2\alpha})$$

For fast alveoli (small α, say 0 5) $V\bar{a}/V_{(T)}$ is 0.88 if $T = 2$ s, and for slow alveoli ($\alpha = 2$, say) $V\bar{a}/V_{(T)} = 0.62$. Since the last portion of alveolar gas, $V\text{D}^{aw}$ never passes the lips, only lungs with larger time constants ventilated with large tidal volumes should theoretically be able to exhibit a positive difference between $P\text{E}'_{CO_2}$ and $P\bar{a}_{CO_2}$ that is caused only by a change of $P\text{A}_{CO_2}$ with time

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LE CONCEPT DE L'ESPACE MORT AERIEN EN SE REFERANT TOUT PARTICULIEREMENT AU TEST DE LA RESPIRATION UNIQUE POUR LA MESURE DU GAZ CARBONIQUE

RESUME

Nous présentons une revue et une analyse théorique des facteurs déterminant l'espace mort des voies respiratoires (V_D^{aw}) et l'espace mort alvéolaire (V_D^{alv}), qui sont les deux constituants de l'espace mort physiologique (V_D^{phys}) V_D^{aw} est le volume de gaz se trouvant entre les lèvres et l'interface du gaz alvéolaire/gaz frais, dont l'emplacement est déterminé par le modèle du débit inspiratoire et par la géométrie des voies respiratoires. V_D^{alv} peut être causé par un mélange incomplet du gaz alvéolaire et par une mésalliance associée de $\dot{V}/\dot{Q}$ à l'intérieur des voies respiratoires terminales, par une mésalliance temporale de $\dot{V}/\dot{Q}$ à l'intérieur de ces voies, par une mésalliance spatiale de $\dot{V}/\dot{Q}$ entre ces voies et par un mélange veineux. La plupart des causes de V_D^{phys} sont influencées par le modèle du débit inspiratoire et par le temps disponible pour la diffusion et la répartition du gaz. L'analyse peut être faite à partir du test de la respiration unique (SBT) pour la mesure du gaz carbonique (SBT-CO$_2$) qui est le tracé graphique de la fraction de gaz carbonique des gaz expirés par rapport au volume expiré. Les causes courantes de V_D^{alv} sont associées à une phase III inclinée de SBT-CO$_2$. La combinaison de SBT-CO$_2$ et de la Pa_{CO_2} donne V_D^{phys} et V_D^{alv}. Une phase III inclinée avec un gradient artériel—fin de volume courant de P_{CO_2} implique une compensation par perfusion assurant un vidage anticipé et des alvéoles surventilées

DAS TOTRAUM-KONZEPT MIT SPEZIELLEM BEZUG AUF DEN EINZELATEMZUGSTEST FÜR KOHLENDIOXYD

ZUSAMMENFASSUNG

Wir legen einen Überblick und eine theoretische Analyse der Faktoren vor, die den Luftweg-Totraum (V_D^{aw}) und den Alveolar-Totraum (V_D^{alv}) bestimmen, die beiden Bestandteile des physiologischen Totraums (V_D^{phys}). V_D^{aw} ist das Gasvolumen zwischen den Lippen und der alveolar/Frischgas-Grenzfläche, dessen Lage durch den Einatmungsstrom und die Luftwegegeometrie bestimmt wird. V_D^{alv} kann durch unvollständige alveolare Gasmischung und damit verbundenes $\dot{V}/\dot{Q}$-Missverhältnis innerhalb der respiratorischen Endeinheiten verursacht werden, oder durch raumliches $\dot{V}/\dot{Q}$-Missverhältnis zwischen den Einheiten und der venosen Beimischung. Die meisten Ursachen fur V_D^{phys} werden durch den Einatmungsfluss und die Zeit beeinflusst, die fur Gasdiffusion und Verteilung vorhanden ist. Eine Analyse kann mittels des Einzelatemzugstests für Kohlendioxyd gemacht werden (SBT-CO$_2$), der die Berechnung des Kohlendioxyd-Bruchteils im ausgeatmeten Gas gegenüber dem Ausatmungsvolumen darstellt. Die gemeinsamen Grunde für V_D^{alv} stehen mit einer abfallenden Phase III von SBT-CO$_2$ in Zusammenhang. Die Kombination von SBT-CO$_2$ mit Pa_{CO_2} ergibt V_D^{phys}

und $V\mathrm{D}^{alv}$. Eine abfallende Phase III mit einem negativen arteriellem Endatemvolumensgefälle $P\mathrm{CO}_2$ bedeutet eine Kompensierung fur sich fruh entleerende, uberventilierte Alveolen durch Durchschwemmung.

EL CONCEPTO DE ESPACIO MUERTO, CON REFERENCIA ESPECIAL A LA PRUEBA DE RESPIRACION UNICA PARA DIOXIDO DE CARBONO

SUMARIO

Presentamos una revisión y un análisisteórico que determinan el espacio muerto del conducto de aire, ($V\mathrm{D}^{aw}$), y el espacio muerto alveolar ($V\mathrm{D}^{alv}$), que son los dos constituyentes del espacio muerto fisiológico ($V\mathrm{D}^{fis}$) $V\mathrm{D}^{aw}$ es el volumen de gas comprendido entre los labios y la interconexión entre los alveolos y el gas sin usar, el emplazamiento de la cual se determina por medio de modelos del flujo aspiratorio y de la geometría del conducto de aire. $V\mathrm{D}^{alv}$ puede tener lugar a causa de una imcompleta mezcla de gas alveolar y de la mal adaptación de $\dot{V}/\dot{Q}$ asociada dentro de las unidades respiratorias terminales, por la mal adaptación de $\dot{V}/\dot{Q}$ temporal dentro de las unidades, por la mal adaptación espacial de $\dot{V}/\dot{Q}$ entre las unidades y por la adversa mezcla venosa. La mayoría de las causas de $V\mathrm{D}^{fis}$ vienen influenciadas por el modelo de flujo aspiratorio y por el tiempo disponsible para la difusión y distribución de gas. Pueden efectuarse análisis partiendo de la prueba de respiración única relativa al dióxido de carbono (SBT-CO_2) la cual es la representación de la fracción de dióxido de carbono presente en el gas espirado, en oposición al volumen de aspiración. Las causas comunes de $V\mathrm{D}^{alv}$ vienen asociadas con una fase III de SBT-CO_2 descendiente. La combinación de SBT-CO_2 con Pa_{CO_2} produce $V\mathrm{D}^{fis}$ y $V\mathrm{D}^{alv}$ Una fase III descendiente con un gradiente negativo en el extremo arterial significa compensación por perfusión para el vaciado temprano del alveolo sobreventilado

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INTRAVASCULAR MIXED VENOUS OXYGEN TENSION MONITORING

An analysis of electrode performance in 100 patients

R. F. ARMSTRONG, J. MOXHAM, S. L. COHEN AND C. J. VALLIS

SUMMARY

A lengthened umbilical artery catheter incorporating an oxygen electrode (Searle) was flow-guided to the pulmonary artery in 48 out of 62 attempts (77.4%). In the last 70 catheters used, electrode performance was evaluated over a total of 3687 h by comparison with an ABL2 (Radiometer) blood-gas analyser; 654 comparisons were made, of which 255 resulted in recalibration of the electrode output. When sampling intervals were within 6 h, in more than 80% of the comparisons the difference between *in vivo* and *in vitro* measurement was within ±0.4 kPa (±3 mm Hg). Twenty-four electrodes were removed sooner than clinically indicated (mean useful life 48.5 h) because of failure of oxygen or pressure measurements.

The measurement of mixed venous oxygen ($C\bar{v}_{O_2}$) has been described by several workers as an index of body oxygen supply, useful in the management of cardiorespiratory disorders. This is based on the relationship expressed by the re-arranged Fick equation:

$$C\bar{v}_{O_2} = \text{arterial } O_2 \text{ content} - \frac{\text{oxygen consumption}}{\text{cardiac output}}$$

From this equation it can be seen that alteration of mixed venous oxygen content will follow any imbalance between oxygen supply and demand.

In this paper we have analysed the results of a technique used to monitor mixed venous oxygen tension ($P\bar{v}_{O_2}$) continuously with flow-guided catheter oxygen electrodes (probes) inserted percutaneously.

APPARATUS

The oxygen sensor (Parker, Key and Davies, 1971) was a small Clark-type polarographic cell made of a silver anode and cathode separated by dried potassium chloride electrolyte (fig. 1). This cell was mounted at the end of a 5-F double-lumen p.v.c. catheter and the tip dip-coated in polystyrene. Wires from the electrode traversed one lumen of the catheter, the other being used for sampling or pressure monitoring (fig. 2). Once inserted into the blood-stream, liquefaction of the dried electrolyte takes place. A small polarizing voltage was applied to the cell (750 mV) and a current was produced proportional to the oxygen tension of the blood. The response time was 95% in 60 s. The current was amplified and displayed on a meter and chart recorder. To prevent mains leakage current reaching the patient, the display

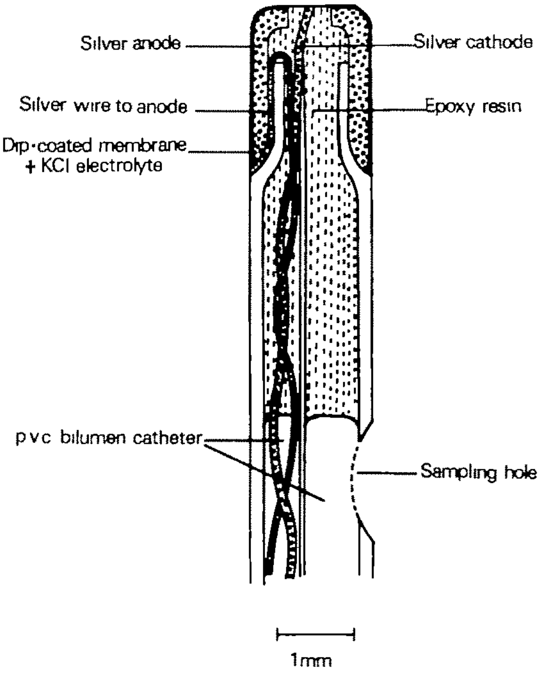

FIG. 1. The catheter-tip Po_2 transducer. (Redrawn after Soutter, Conway and Parker, 1975.)

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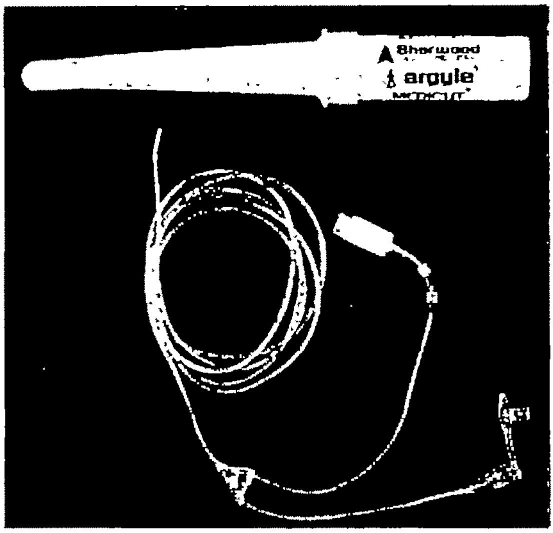

FIG. 2. The catheter with Medicut container for comparison.

meter was powered by batteries and optically isolated from the chart recorder.

The diameter of the probe (5-F) and its length (1 m) allowed percutaneous insertion into the venous system via a 12-gauge cannula from antecubital or periclavicular sites. Although the catheter had no distal balloon, its lightness and flexibility allowed it to be drawn centrally by the venous blood flow. Its position was verified by recording pressure wave forms via the sampling lumen and in this way placement in the heart was achieved without recourse to x-ray screening.

For use during insertion we have designed a small collar which can be slipped into the hub of a Medicut cannula. The catheter passed through this collar smoothly and in this way peri-catheter blood loss or air entry during insertion was prevented (fig. 3).

After placement of the probe a check x-ray was performed to verify position and exclude pneumothorax. Subsequently, samples of blood were withdrawn from the sampling lumen of the probe and oxygen tension measured by blood-gas analysis. Once a stable output was obtained the meter display and chart recorder could be calibrated. We have found it useful to record heart rate continuously as any significant change in $P\bar{v}_{O_2}$ is usually associated with a change in heart rate.

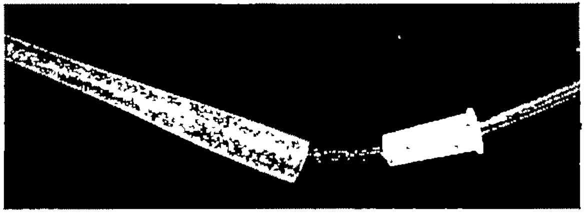

FIG 3. Close-up of catheter collar.

PATIENTS

Patients in the Intensive Care Unit at University College Hospital were studied. Initially all patients had acute pulmonary insufficiency. Subsequently, the indications were extended to include high-risk surgical and medical cases (including myocardial infarction). Ethical committee approval, informed consent from patients or relatives and agreement from the consultant in charge were obtained. Two volunteers (R. F. A. and J. M.) were catheterized also.

RESULTS

Catheter placement

There were 62 attempts at pulmonary artery placement, of which 48 were successful (77.4%). Where pulmonary artery placement failed or was judged potentially dangerous right atrial positioning was chosen (38 patients). Insertion was achieved easily and without discomfort. There were occasional extrasystoles during passage through the ventricle and there was one case of supraventricular tachycardia which reverted to sinus rhythm on removal of the catheter. One catheter developed a redundant loop in the ventricle and became knotted, but withdrawal was accomplished without difficulty. Three patients developed signs of mild skin infection at the antecubital site of insertion.

Activation

Once in the circulation, activation of the polarographic cell began. The time taken to develop a stable output differed between electrodes (fig. 4).

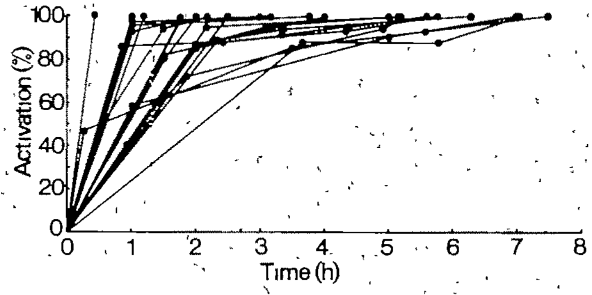

FIG. 4. Time-course of activation of 20 *in vivo* catheters.

For the purpose of calibration we did not consider the probes to have reached a stable output until approximately 4 h after insertion. Where quicker function is required pre-activation can be achieved by injection of sterile saline into the packet or by immersion of the electrode in a sterile saline-filled container.

Accuracy

The study was divided into a pilot group of 30 catheters and a main group of 70. During the pilot study there was a steady improvement in catheter management as evaluation of the results identified operator errors. For this reason only the 70 catheters used in the main study were used to assess accuracy. These were used for a total of 3687.8 h. During this time 654 paired observations were made of catheter (probe) reading *v. in vitro* analysis by an ABL2 blood-gas analyser using samples taken from the sampling lumen. Quality checks of our ABL2 are made at weekly intervals in accordance with the manufacturer's recommendations.

Table I summarizes the paired observations in a correlation table and gives the frequency distributions of observations from each source. The diagonal line indicates agreement between the two readings and the scatter reflects the measurement error.

Table II shows the 654 observations grouped according to the interval from the preceding observation, up to 2 h, 2–3.9 h, 4–5.9 h, 6–11.9 h and 12 h or more. The distribution of the differences in $P\bar{v}_{O_2}$ (electrode minus analyser) has been derived for each of the above five sampling intervals and overall. For each group the mean difference, the standard deviation (SD) and the standard error of the mean (SEM) are quoted, with the significance of the difference of the mean from zero.

These results demonstrate that if sampling intervals are kept shorter than 6 h then more than 80% of the differences should fall within the range ±0.4 kPa (±3 mm Hg). Because there is an increase in mean difference with increase in sampling intervals, this suggests a positive drift on the part of the probe, although of such magnitude to be of no great consequence.

Probe function

Of the 70 probes used in the main study 35 were removed earlier than indicated. The reasons for removal are summarized in table III. Seven probes were damaged by excessive traction during nursing manoeuvres such as lifting. Three probes were removed because of minor skin infection at the entry site. One probe was calibrated incorrectly and generally mishandled and this was classified as user error. Of the removals because of failure of probe function as opposed to operator error, one gave no satisfactory pressure trace, three failed to activate and three developed sampling lumen blockage, making calibration impossible. Finally, eight catheters developed marked swing or drift in electrical output and a further 10 eventually developed total loss of output.

The overall mean useful life of the "failed" catheters was 48.5 h.

DISCUSSION

The pulmonary artery is recognized traditionally as the only source of true mixed venous blood, although attention has been drawn (Suter et al., 1975) to the inaccuracy in $C\bar{v}_{O_2}$ measurement which can result from sampling too quickly or from too distal a position. In this series the success rate in flow-guiding the catheters to the pulmonary artery (77.4%) compares unfavourably with Swan and others (1970), perhaps reflecting the loss of traction produced by the absence of a balloon at the catheter tip. However, where pulmonary artery placement was not possible we accepted a mid right-atrial position in view of the close correlation (Scheinman, Brown and Rapaport, 1969; Lee et al., 1972) described between samples from this site and the pulmonary artery and from our own observations of the similarity of recordings obtained simultaneously from the two sites.

Accuracy

In order to evaluate the performance of the probes, their duration of useful life was determined retrospectively from the sequence of routine paired observations. This period extended from the moment the probes had developed a stable output up to the time that the life of the probe was completed by withdrawal, damage, loss of output or the onset of erratic output (swing or drift). For 70 probes a total of 3687.8 h of monitoring has been studied during which time 654 samples were taken for blood-gas analysis.

Comparison of these paired observations is shown in the correlation table (table I). The scatter reflects measurement error which may be present

TABLE I. *Distribution of $P\bar{v}_{O_2}$ values and relationship between monitor and analyser results. Values given on axes in mm Hg*

Monitor $P\bar{v}_{O_2}$	Analyser $P\bar{v}_{O_2}$ 20–21	22–23	24–25	26–27	28–29	30–31	32–33	34–35	36–37	38–39	40–41	42–43	44–45	46–47	48–49	50–51	52–53	54–55	56–57	58–59	60–61	62–63	64–65	Total
20–21	2																							2
22–23		1	1			2																		4
24–25			1	2	1	1			1															6
26–27			2	10	8	2	1																	23
28–29				6	8	10	6				1													31
30–31				3	9	19	10	4																45
32–33				2	4	7	18	12	7	5	1													56
34–35					1	3	20	33	12	4	8	1												82
36–37							13	18	35	13	5	2	1											87
38–39						1	2	13	21	26	18	9	1	1	1									93
40–41								2	17	21	20	8	4			1								73
42–43								2	5	9	13	13	5	2										49
44–45						1		1	1	6	4	14	10	2										39
46–47									1	2	2	4	5	5	5									24
48–49						1				1		1	2	3	2	2	1							13
50–51											1			5	3	4	1							14
52–53												1			3	1	1							6
54–55																								
56–57													1											1
58–59																								
60–61													1	1										2
62–63													1			1			1					3
64–65																								
66–67																							1	1
Total	2	1	4	23	31	47	70	85	100	87	73	53	31	19	14	9	3		1				1	654

TABLE II. *Difference (mm Hg) between monitor and analyser $P\bar{v}_{O_2}$ results during routine monitoring (monitor minus analyser). Distribution by interval from previous observation and related to frequency of recalibration*

	Interval from previous paired observation, t (h)					Overall	
Difference (mm Hg)	<2	$2 \leqslant t < 4$	$4 \leqslant t < 6$	$6 \leqslant t < 12$	$t \geqslant 12$	Total	No. of resulting recalibrations
−13				1		1	1
−12		1				1	1
−11		1				1	1
−10		1				1	1
−9						1	1
−8	1		2	1	2	6	5
−7		2				2	2
−6	1	1	1	4	1	8	6
−5	2	1	2	4	3	12	10
−4	4	8	6	3	2	23	18
−3	6	9	9	5	2	31	20
−2	15	12	17	8	5	57	28
−1	18	20	22	13	6	79	8
0	25	40	26	19	15	125	1
1	15	27	30	11	6	89	8
2	12	22	16	16	5	71	30
3	6	14	15	13	6	54	40
4	8	6	3	14	7	38	29
5	5	5	3	7	3	23	18
6	2	5	3	3		13	12
7		1				1	1
8			3	1	1	5	3
9				1		1	1
10		1	2		2	5	5
11					2	2	2
12							
13				1		1	1
14							
15				1		1	1
16					1	1	
17				1	1	2	2
Total (*n*)	120	177	160	127	70	654	255
Mean	+0.17	+0.27	+0.36	+1.04	+1.33	+0.54	
SD	2.57	3.00	2.87	3.99	4.68	3.34	
SEM	0.23	0.23	0.23	0.35	0.56	0.13	
Significance (mean *v.* zero)	n.s.	n.s.	n.s.	$P = 0.004$	$P = 0.020$	$P = 0.00005$	
Percent within range −3 to +3	80.8	81.4	84.4	66.9	64.3	77.4	

in both probe and ABL (Selman and Tait, 1976) and which may be influenced by sampling frequency and technique (Suter et al., 1975), time of transportation of sample (Scott, Horton and Mapleson, 1971), *in vivo* and *in vitro* temperature differences (Adams, Morgan Hughes and Sykes, 1967) and failure to allow for the response time of the probe (Wilkinson, Phibbs and Gregory, 1979). Our results can be compared with those of two other groups who have used this *in vivo* oxygen electrode for continuous arterial $P\text{O}_2$ measurement in neonates (Conway et al., 1976; Wilkinson, Phibbs and Gregory, 1979). These investigations describe correlation coefficients of 0.97 and 0.948 respectively between *in vivo* and *in vitro* measurements. Examination of the diagrams in these studies showing the distribution of simultaneous measurements by probe and blood-gas analysis

TABLE III. *Reasons for probe removal, and probe lives*

Reason for probe removal	No.	Mean useful life (h)
No longer required		
Patient recovered	23	82.65
Patient died	13	32.65
Total	36	64.63
Clinical use related		
Accident	7	53.31
Infection	3	25.43
Mistake	1	0
Total	11	40.86
Performance related		
No pressure trace	1	0
Failure to activate	3	0
Swing or drift	8	45.6
Loss of output	10	37.49
Lumen blockage	3	93.1
Total	24	48.5
Overall	71	52

shows that 95% of *in vivo* readings fall approximately within ±2.4 kPa (±18 mm Hg) of a given *in vitro* result. Where attention is paid to the response time of the probe, this has been reduced to ±1.5 kPa (±11.5 mm Hg). For our application of the probe, 95% *in vivo* readings fall within ±0.67 kPa (±5 mm Hg) of the *in vitro* $P\bar{v}_{O_2}$ result, perhaps reflecting the greater stability of venous as opposed to arterial oxygenation.

Probe life

The mean useful life of the probes used in this series was 52 h. Excluding operator error (accidental traction and infection) there were 25 probes which failed after a mean useful life of 48.5 h. Three of these failed to activate. This was probably because of membrane adherence to the electrode tips as a consequence of a now abandoned *in vitro* test procedure carried out by the manufacturer before release. Eight developed erratic output having functioned satisfactorily for a mean time of 45.6 h. Two of these were found to have loose wiring when examined after removal. A further 10 probes developed sudden and complete loss of output, thought to be a result of clotting on the electrode tip after a mean useful life of 37.5 h. Overall, 29.5% of our probes developed technical (as opposed to management) problems. This can be compared with the experience of Pollitzer and others (1980) who describe a frequency of catheter failure of 33.6% in 268 probes used in neonatal monitoring. A probe life-curve plotting the percentage of probes performing satisfactorily after a given time *in situ* indicates a 50% (±16%) probability of a probe performing satisfactorily for 5 days. At 2 and 3 days the probabilities are 78% (±11%) and 62% (±14%) respectively. Improvements in manufacturing techniques and management of the probe may improve these figures, which cover a 3-yr period of analysis.

Value of $P\bar{v}_{O_2}$ monitoring

The significance of mixed venous oxygen measurements has yet to be defined exactly. Several workers (Boyd et al., 1959; Goldman et al., 1968; Stanley and Isern-Amaral 1974; Krauss et al., 1975) have demonstrated its value in the prediction and early recognition of deteriorating cardiac function and systemic perfusion, although without showing a linear correlation with cardiac output (Parr, Blackstone and Kirklin, 1975). Comparison with venous lactate measurement (Kasnitz et al., 1976; Simmons et al., 1978) suggests that a low $P\bar{v}_{O_2}$ may be a useful index of poor tissue oxygen supply and there is evidence that tissue PO_2 measured by indwelling electrodes correlates well with $P\bar{v}_{O_2}$ (Hiller and Bone, 1978). However, the theoretical value of $P\bar{v}_{O_2}$ as a simple expression of the balance between oxygen supply and demand is not straightforward. Experimental work with anaesthetized and paralysed dogs (Cain, 1977) shows that the onset of deterioration in oxygen uptake occurs at widely different values of mixed venous oxygen tension during anaemic and hypoxic hypoxia. Calculated total oxygen delivery, however, was very similar in both groups as oxygen uptake failed, suggesting that volume delivery rates may be more important than delivery PO_2 and that, during anaemia, tissue hypoxia could occur at normal mixed venous oxygen tensions.

Shifts in the oxyhaemoglobin dissociation curve may also serve to obscure the meaning of $P\bar{v}_{O_2}$ changes, as does functional shunting of blood by overperfusion of areas with low oxygen uptake. Nevertheless, with the exception of two cases of septicaemia our experience is that $P\bar{v}_{O_2}$ correlates well with the clinical condition of the patient (Moxham and Armstrong, 1981) and provides a continuous and valuable measure of oxygenation as influenced by pulmonary and cardiac function as well as oxygen uptake. In particular, the method allows identification of a group of patients especially sensitive to physical movement or arterial hypoxaemia. In these patients major and sustained decreases in $P\bar{v}_{O_2}$ (Armstrong et al., 1978) suggest a failure of normal compensatory response which may pass unnoticed during standard intermittent monitoring techniques. With clarification of the factors affecting $P\bar{v}_{O_2}$ and improvements in probe performance, methods of this sort should prove to be a useful adjunct to current monitoring techniques, perhaps in combination with pulmonary artery catheters of the Swan–Ganz type.

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CONTROLE DE LA TENSION MIXTE DE L'OXYGENE DONNEE INTRAVASCULAIRE

Analyse de performances des électrodes sur 100 patients

RESUME

Un catéther pour artère ombilicale rallongé et comportant une électrode d'oxygène (Searle) a été introduit dans le sens du débit sanguin de l'artère pulmonaire dans 48 essais sur 62 (77,4%). Dans les 70 derniers catéthers utilisés, on a évalué les performances de l'électrode sur un total de 3686 h, par comparaison avec un analyseur de sang-gaz ABL2 (Radiometer); 654 comparaisons ont été faites, dont 255 ont eu pour résultat de faire procéder à un ré-étalonnage du débit de l'éléctrode. Lorsque les intervalles d'échantillonnage se situaient à l'intérieur d'une péroide de 6 h, et dans plus de 80% des comparaisons, la différence entre les mesures prises *in vivo* et *in vitro* se sont situées dans les limites de ±0,4 kPa (±3 mm Hg) Vingt-quartre électrodes ont été retirées plus tôt que cliniquement indiqué (vie utile moyenne 48,5 h), en raison des erreurs de mesure de l'oxygène ou de pression.

INTRAVASKULÄRE GEMISCHT-VENÖSE SAUERSTOFFSPANNUNGSKONTROLLE

Eine Analyse der Elektrodenleistung bei 100 Patienten

ZUSAMMENFASSUNG

Eine verlangerter Nabelschnurarterien-Katheter mit einer Sauerstoffelektrode (Searle) konnte in 48 von 62 Versuchen (77,4%) im Blutstrom zur Lungenarterie gebracht werden. In den letzten 70 verwendeten Kathetern wurde die Leistung der Elektroden über insgesamt 3686 Stunden beurteilt—im Vergleich zu einem Blutgas-Analyseapparat ABL2 (Radiometer); 654 Vergleiche wurden angestellt, von denen 255 zu einer Neueichung des Elektrodenausganges fuhrten. Wenn die Probenintervalle sich innerhalb von 6 Stunden bewegten, war bei mehr als 80% der Vergleiche der Unterschied zwischen Messungen *in vivo* und *in vitro* innerhalb von ±0,4 kPa (±3 mm Hg). Vierundzwanzig Elektroden wurden fruher als klinisch angezeigt entfernt (mittlere nutzliche Lebensdauer 48,5 Stunden), weil es zu einem Versagen der Sauerstoff- oder Druckmessungen kam.

VIGILANCIA DE LA TENSIÓN DEL OXÍGENO MEZCLADO, VENOSO E INTRAVASCULAR

Un análisis del funcionamiento de electrodo en 100 pacientes

SUMARIO

Un catéter umbilical y alargado para uso en arterias, que incorporaba un electrodo de oxígeno (Searle) se guió por flotación hasta la arteria pulmonar en 48 de los 62 intentos efectuados (77,4%). En los 70 últimos catéter usados se evaluó el funcionamiento del electrodo durante más de 3686 h, en comparación con un analizador de gas sanguíneo ABL2 (Radiometer); se efectuaron 654 comparaciones de las que 255 necesitaron la recalibración de la salida del electrodo En más del 80% de las comparaciones efectuadas, la diferencia entre las mediciones *in vivo* e *in vitro* presentó una tolerancia de ±0,4 kPa (±3 mm Hg), cuando los intervalos de muestreo eran iguales o inferiores at 6 h. Se extrajeron 24 electrodos antes de lo clínicamente prescrito (vida media útil 48,5 h) a causa del fallo del oxígeno o de las mediciones de presión.

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A STUDY OF INTRACUFF PRESSURE MEASUREMENTS, TRENDS AND BEHAVIOUR IN PATIENTS DURING PROLONGED PERIODS OF TRACHEAL INTUBATION

L. JACOBSON AND R. GREENBAUM

SUMMARY

Intracuff pressure (c.p.) was measured continuously in 12 patients during prolonged periods of tracheal intubation. High residual volume–low pressure (floppy) and low residual volume–high pressure (conventional) cuffs were studied. The mean baseline c.p. at minimal occluding pressure was significantly smaller in floppy cuffs than in conventional cuffs. With coughing, the peak pressures in both cuff types were much greater than the baseline pressures but did not differ significantly from each other. On the basis of our observations, we recommend a simplification of the test methods for cuffs and tube collapse. We believe universal testing to 300 mm Hg (40 kPa) to be reasonable and to incorporate a realistic safety factor. Intracuff pressure tends to diminish with time, but there is a poor correlation between the rate of pressure decrease and elapsed time. As this decrease is not accurately predictable, gas should be added to the cuff as required, rather than at regular intervals. Other features of cuff behaviour are discussed and suggestions made to explain some anomalies occasionally observed in the cuff pressure behaviour pattern.

The value of endotracheal and tracheostomy tube cuffs in reducing the risk of erratic ventilation of the lungs and of aspiration has been appreciated since the poliomyelitis epidemic in Copenhagen in 1952 (Lassen, 1953; Ibsen, 1954; Safar et al., 1962; Carroll, Heddon and Safar, 1969). However, cuffs may cause complications (Cooper and Grillo, 1972). Investigators, designers and manufacturers issued a joint statement recommending performance specifications for cuffed endotracheal and tracheostomy tubes (Carroll et al., 1973; Carroll, McGinnis and Grenvik, 1974), aiming for a product design which minimizes the possibility of misuse and provides for continued safe function. In an attempt to attain the requirements, the British Standards Institute and the International Organization for Standardization have been working to develop a standard for tracheal tubes and cuffs for prolonged use. Such a standard would incorporate methods of test for cuffs and tube collapse in an attempt to minimize the possibility of failure in clinical use.

The studies reported in this paper were undertaken to determine c.p. generated during prolonged tracheal intubation. Information on this subject has been sparse and difficulties have arisen in determining a test pressure which incorporates a realistically agreed safety factor.

METHODS

Commercially available tracheal and tracheostomy tubes (Portex) were studied. Intracuff pressures were measured in patients in an intensive therapy unit (ITU) over a variable period depending on the duration of intubation. Both high residual volume–low pressure (floppy) and low residual volume–high pressure (conventional) cuffs were assessed.

The apparatus consisted of a four-way stopcock attached to a fluid filled tube and connected to a SEM 4-88 strain gauge physiological pressure transducer, which was plugged into a SE-4000 multi-channel amplifier system. The pressures were recorded on a two-channel felt-tip pen recorder.

The stopcock was connected to the pilot tube of the cuff system. The expired gas mixture was used to inflate the cuff to the minimum occluding pressure (m.o.p.) as determined by the absence of breath sounds over the neck and at the mouth on auscultation with a stethoscope.

The transducer trolley was kept at the level of the manubrio–sternal junction. Intracuff pressure was measured continuously and recorded. All patients had relatively constant body temperatures in the normothermic range.

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Sedative drugs were used in preference to neuromuscular blocking drugs to facilitate intermittent positive pressure ventilation of the lungs.

RESULTS

Mean baseline c.p. in conventional cuffs was 61 mm Hg (table I). This was significantly greater than in the floppy cuff tubes in which the mean pressure was 24 mm Hg (table II) ($P<0.01$).

TABLE I. *Low residual volume, high pressure cuffs. Baseline pressures and peak intracuff pressures*

Patient	Baseline pressure (mm Hg)	Peak pressure (mm Hg)	Difference
1	110	168	+58
2	50	105	+55
3	30	60	+30
4	75	170	+95
5	50	100	+50
6	50	170	+120
$\bar{x}$	61	129	68
SD	26	43	30
SEM	10	18	12

TABLE II. *High residual volume low pressure cuffs Baseline pressures and peak intracuff pressures*

Patient	Baseline pressure (mm Hg)	Peak pressure (mm Hg)	Difference
1	23	133	+110
2	45	120	+75
3	15	115	+100
4	34	80	+46
5	15	56	+41
6	13	155	+142
$\bar{x}$	24	110	+86
SD	12	33	36
SEM	5	13	15

The mean peak c.p. observed in conventional and floppy cuffs were 129 mm Hg and 110 mm Hg respectively (tables I and II). Both were significantly greater than the baseline pressures ($P<0.01$). There was no significant difference between the peak pressures in the cuffs ($P>0.1$) or between the differences between baseline and peak pressures for floppy and conventional cuffs ($P>0.1$) (fig. 1).

C.p. decreased with time. However there was no significant correlation between the cuff pressure decrease and time. Tables III and IV show that

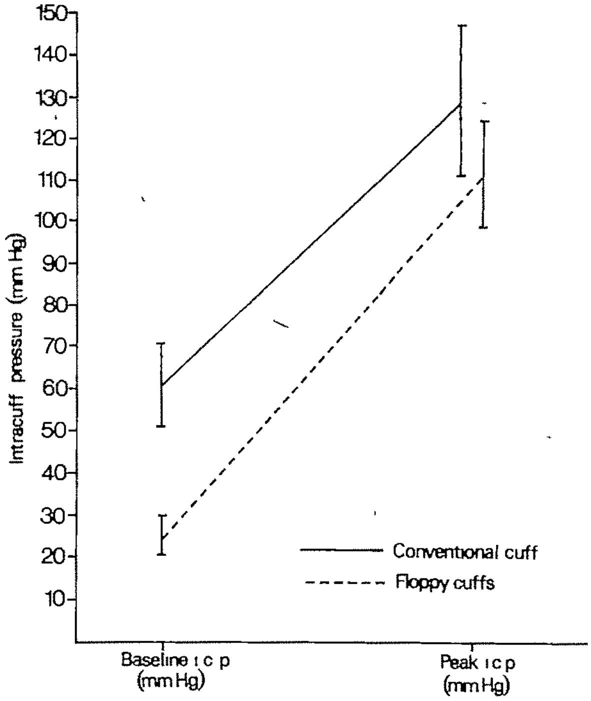

FIG. 1. Comparison of the increase in c.p. with coughing. Bars represent SEM.

TABLE III. *Low residual volume, high pressure cuffs. Decay of c.p. with time.* $r = -0.73$

Patient	Initial c.p. (mm Hg)	Terminal c.p. (mm Hg)	Difference	Time (h)
1	110	60	−50	17
2	95	75	−20	6
3	30	20	−10	10
4	65	25	−40	30
5	30	20	−10	6
$\bar{x}$			−26	

TABLE IV. *High residual volume, low pressure cuffs. Decay of c.p. with time.* $r = -0.65$

Patient	Initial c.p. (mm Hg)	Terminal c.p. (mm Hg)	Difference	Time (h)
1a	23	15	−8	6
1b	20	5	−15	12
2	20	5	−15	9
3	34	20	−14	6
4a	15	5	−10	10
4b	45	28	−17	10
5	20	20	0	6
6	16	10	−6	6
$\bar{x}$			−10.56	

$r = -0.73$ for conventional cuffs ($P > 0.1$) and -0.65 for floppy cuffs ($P > 0.05$) respectively.

DISCUSSION

The study demonstrates significant transient increases in c.p. with coughing. Other manoeuvres, such as neck flexion, extension and rotation, have little effect. Peak pressures of 170 mm Hg and 155 mm Hg have been observed in conventional and floppy cuffs respectively.

A recommended test for cuffs and tubes involves the measurement of baseline m.o.p. with the tube in an artificial trachea. An inflation pressure of between 100 and 300 mm Hg is used, depending on m.o.p., and cuff asymmetry, herniation and tube collapse sought. However, we found no constant relationship between baseline c.p. and peak c.p. There was no significant difference between peak c.p. of conventional and floppy cuffs despite the marked disparity in their baseline pressures. On occasions, the peak c.p. exceeded that which would be anticipated for the baseline pressures observed, according to the approved test tables. This could result in tubes being tested at inflation pressures less than those which may be encountered clinically. We suggest the use of a standard inflation pressure test, irrespective of the cuff type. Universal testing to a pressure of 300 mm Hg should suffice.

We believe that this will include conditions likely to be encountered in clinical practice, provided certain elementary clinical rules are observed when selecting and managing cuffed tubes (Cooper and Grillo, 1972; Carroll, 1973; Carroll, McGinnis and Grenvik, 1974).

Intracuff pressures tend to decrease with time, probably as a result of a combination of slow movement ("creeping") of the plastic cuff material and diffusion of gases. By movement, the cuffs may stretch and increase their volume, thereby decreasing the pressure (McGinnis et al., 1971; Hill, 1976). Nevertheless there is no predictable rate of pressure decrease ($P > 0.05$). The clinical implication is that, should c.p. decrease to less than 15–25 mm Hg, aspiration past the cuff would be a hazard (Carroll, 1973; Bernhard et al., 1979). A significant cuff leak in a patient receiving intermittent positive pressure ventilation may cause inadequate ventilation (Carroll, Heddon and Safar, 1969).

Cross (1973) and Crawley and Cross (1975) studied the relationships applicable to various inflatable cuff systems *in vivo*, and demonstrated the importance of cuff diameter and the stiffness of cuff material in the ultimate determination of both c.p. and tracheal wall pressure. They studied the applied physiology and physics of conventional and floppy cuff systems and their relationship to airway pressure. Our unpublished findings endorse their work. It is of interest to note that the mean baseline c.p. in conventional cuffs (61 mm Hg) was much greater than in the floppy type (24 mm Hg).

We have occasionally recorded c.p. values, in conventional cuffs, in the range associated with the low pressure variety. Several factors probably occur simultaneously. The moist warm environment in the trachea alters the consistency of the cuff material and promotes movement of the plastic. Repeated episodes of increased c.p. compress the cuff material and contribute to the movement phenomenon observed in plastic materials. The effect may resemble that encountered by prestretching cuffs (Geffin and Pontoppidan, 1969). If an appropriately sized conventional cuffed tube is inserted, c.p. in the range seen in floppy cuffed tubes may be recorded, especially after a period of time.

Occasionally c.p. in floppy cuffs was greater than expected. This may be related to the formation of longitudinal folds along the length of the cuff because its circumference is greater than that of the trachea. Leakage may occur along these folds even when c.p. is equal to the inflation pressure. Thus the cuff may have to be inflated to the extent where the tracheal wall pressure exceeds the capillary pressure (Cross, 1973; Crawley and Cross, 1975). Also, the resting size of the cuff concerned may be too small for the trachea, requiring it to be over-expanded in the trachea in order to create a seal. Such a cuff has a low pressure only at a volume insufficient to form a seal and becomes a rigid high pressure cuff as it distends to the sealing volume.

The significant transient increases in c.p. that occur with coughing are unlikely to be exclusively a result of the cuff being compressed by the increased intrathoracic pressure. These peak pressures are usually generated when coughing is initiated by suction through the endotracheal tube, which is therefore open to the atmosphere at the time, thus precluding a large increase in intrathoracic pressure. More plausible is that a moderately increased intrathoracic pressure, generated by the cough, acts on the trachea, which is a dynamic organ, and causes it to alter its configuration and to constrict the cuff (Croteau and Cook, 1961; Scarpelli, Real and Rudolph, 1965; Carroll, McGinnis and Grenvik, 1974). These conditions of cuff compression approach those of non-distensibility and the pressure increases as the volume is diminished because of tracheal compression.

We observed no simple relationship between the strength of cough and the peak cuff pressure reached. This depends on other factors such as the tracheal compliance, degree of altered intrathoracic pressure, the extent of cuff inflation, the diameter of the cuff in relation to the trachea and the stiffness of the cuff material. Therefore it cannot be concluded that patients with the most active cough will generate the greatest peak pressures. These peak c.p. pose a potential hazard of tube collapse, cuff herniation and cuff asymmetry. Thus it is important that an agreed standard for tracheal tubes and cuffs for prolonged use be determined.

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ETUDE DE MESURES, DES TENDANCES ET DU COMPORTEMENT DE LA PRESSION INTRAMANCHON SUR DES PATIENTS SOUMIS A UNE INTUBATION TRACHEALE

RESUME

On a mesuré d'une manière continue, sur 12 patients et pendant des périodes prolongées d'intubation trachéale, la pression se trouvant à l'intérieur du manchon (c.p.). On a étudié les manchons présentant un important volume résiduel-basse pression (trop large) et les manchons ayant un faible volume résiduel et une haute pression (normaux). La c.p. moyenne de base, à la pression d'occlusion minimale, a été sensiblement plus faible dans les manchons trop larges que dans les manchons normaux. Lorsque les patients ont toussé, les pressions de pointe, dans les deux types de manchons, ont été beaucoup plus importantes que les pressions de base mais elles n'ont tout de même pas varié d'une manière significative, les unes par rapport aux autres. En nous basant sur nos observations, nous pouvons recommander une simplification des méthodes d'essai des manchons et des déformations de tubes. Nous estimons que les essais universels à 300 mm Hg (40 kPa) sont raisonnables et comprennent un facteur de sécurité réaliste La pression à l'intérieur du manchon tend à diminuer avec le temps, mais la corrélation entre le rythme de la baisse de pression et le temps écoulé est mauvaise Comme cette baisse n'est pas prévisible d'une manière précise, il faudrait ajouter du gaz au manchon en fonction des besoins, plutôt qu'à des intervalles réguliers. On expose dans ce document d'autres caractéristiques sur le comportement des manchons et on y fait des suggestions pour expliquer certaines anomalies que l'on a occasionnellement observées dans le modèle de comportement de la pression du manchon.

STUDIE VON MANSCHETTEN-INNENDRUCKMESSUNGEN; TRENDS UND VERHALTEN VON PATIENTEN WÄHREND LÄNGERER PERIODEN VON TRACHEALROHREINFÜHRUNG

ZUSAMMENFASSUNG

Der innere Manschettendruck (c.p.) wurde kontinuierlich während langerer Perioden von Trachealrohreinführung gemessen. Manschetten mit hohem Restvolumen-niedrigem Druck (weich) und mit niedrigem Restvolumen-Hochdruck (konventionell) wurden studiert. Der mittlere Ausgangswert von c.p. bei minimalen Staudruck war in weichen Manschetten wesentlich geringer als in konventionellen. Bei Husten waren die Spitzendrücke in beiden Manschettenarten wesentlich höher als die Ausgangsdrücke, unterschieden sich aber nicht wesentlich voneinander. Aufgrund unserer Beobachtungen empfehlen wir eine Vereinfachung der Testmethoden fur Manschetten. Wir halten eine universelle Prüfung auf 300 mm Hg (40 kPa) fur angemessen, und für einen realistischen Sicherheitsfaktor. Der innere Manschettendruck neigt mit der Zeit zur Verringerung, doch gibt es kaum eine Korrelation zwischen der Rate dieses Druckabstieges und der dabei vergangenen Zeit. Da dieser Abstieg nicht prazise voraussagbar ist, sollte Gas je nach Bedarf den Manschetten zugefuhrt werden—nicht in regelmässigen Abständen. Andere Eigenschaften des Verhaltens der Manschetten werden diskutiert, und es werden Erklärungsvorschlage für manche Anomalien gemacht, die gelegentlich im Druckverhalten von Manschetten beobachtet werden.

UN ESTUDIO DE LAS MEDICIONES DE LA PRESIÓN INTRAYUGO, DE LAS PROYECCIONES Y DE LA CONDUCTA DE LOS PACIENTES DURANTE PROLONGADOS PERIODOS DE INTUBACIÓN TRAQUEAL

SUMARIO

Se midió de modo continuo en 12 pacientes la presión intrayugo, durante prolongados periodos de intubación traqueal. Se estudiaron yugos con un alto volumen residual y baja presión (sueltos) y de bajo volumen residual y alta presión (convencional). La línea media de base relativa a la presión intrayugo, a la mínima presión de oclusión, fue singificativamente más pequeña en yugos sueltos que en los convencionales. Al toser, las presiones de cresta en ambos tipos de yugos fueron mucho mayores que las de la línea de base, pero no se diferenciaron entre sí de modo significativo. Con base en nuestras observaciones, recomendamos una simplificación de los métodos de verificación para el colapso del tubo y del yugo. Consideramos razonable la verificación universal con arreglo a 300 mm Hg (40 kPa) y el incorporar un factor de seguridad realista. La presión intrayugo tiende a disminuir con el tiempo pero existe una deficiente correlación entre el régimen de disminución de la presión y el tiempo transcurrido. Dado que esta disminución no puede predecirse con precisión, debe añadirse gas al yugo según se requiera, en vez de a intervalos regulares. Se discuten otras características del yugo y se efectúan sugerencias para explicar ciertas anomalías que a veces se observan en los modelos de conducta de la presión de los yugos.

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RESPIRATORY MASS SPECTROMETRY DURING GENERAL ANAESTHESIA

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SUMMARY

The performance of a respiratory mass spectrometer, modified commercially for use during general anaesthesia, has been evaluated. Stability and linearity proved satisfactory for monitoring respiratory gases and accurate measurement was possible when the inspired concentration of all gases was less than 80%. The system has been installed centrally in a three-room operating theatre suite and the selection of long sampling probes which permit an adequate response time for all gases is discussed.

Respiratory mass spectrometers suitable for clinical use have been available for a number of years, but their value during anaesthesia has been limited until recently because the spectra of several anaesthetic gases and vapours overlap those of the respiratory gases. Thus, nitrous oxide and carbon dioxide have the same molecular weight (44) and both are detected by mass spectrometry at this mass number, while halothane (mol. wt 197.4) is fragmented in the ionizing chamber of the spectrometer to produce, amongst others, charged particles which generate signals at mass numbers close to those of both oxygen and carbon dioxide. This problem has been resolved by Davis and Spence (1979) who have described a spectrum overlap eraser which allows quantitative measurement of individual gases in a mixture when several contribute to the signal detected at one or more of the mass numbers. The principle of this modification is that nitrous oxide and volatile anaesthetics fragment in a fixed proportion within the mass spectrometer; provided at least one fragment can be detected as the sole output at a particular mass number, the proportion of the parent substance in the original gas mixture can be determined, as well as the contribution made by the parent substance to the outputs detected at the mass numbers of the respiratory gases. Subtraction circuits are used to eliminate these unwanted signals so that the output voltages detected at mass numbers 28, 32 and 44 are proportional to the fractional concentrations in the original mixture of nitrogen, oxygen and carbon dioxide respectively.

This system is now available commercially and the performance of such an instrument, installed centrally in a three-room operating suite, is reported here. The validity of recording through the long probes which are used to convey samples from several sites to a centrally-situated mass spectrometer has been reported previously (Davies and Denison, 1979; Gothard et al., 1980).

The mass spectrometer

The Centronic MGA 200 mass spectrometer modified for use during anaesthesia is an eight-channel quadrupole instrument with four anaesthetic correction circuits. Three calibrated, 10-turn helical potentiometers on each of the four channels allow subtraction of the following signals:

channel 1, nitrogen, (28): nitrous oxide, carbon dioxide and volatiles;
channel 2, oxygen, (32): nitrous oxide, carbon dioxide and volatiles;
channel 3, carbon dioxide, (44): nitrous oxide, oxygen and volatiles;
channel 4, nitrous oxide, detected as nitric oxide at mass 30: oxygen, volatiles and spare.

The automatic summing circuit (automatic sensitivity control; automatic stability control; ASC) has been retained and operates on the output voltages after the overlapping signals have been eliminated. It corrects automatically for alterations in sensitivity, barometric pressure or water vapour so that the total output voltage from the selected channels remains constant (Scheid, Slama and Piiper, 1971).

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The instrument has been installed in a room approximately 2.5 × 1.8 m which opens off the theatre disposal corridor and which also houses cylinders of calibrating gases, an oscilloscope and recording apparatus. Heat generated in this room, primarily by the mass spectrometer, has necessitated independent air conditioning to maintain a temperature within the operating range of the mass spectrometer (22–27 °C).

The sampling system

Four long probes (15, 20 or 25 m) of "Portex" 1-mm i.d. polyethylene tubing pass from the mass spectrometer through specially installed ductwork to each of three operating rooms where they terminate in Luer-connectors mounted in a wall panel close to the outlets for the piped gas supplies. At present, selected probes are joined to one of the two gas inlet ports of the mass spectrometer, but eventually a valve box and switching mechanism (Gothard et al., 1980) will be installed so that samples from up to 12 probes can be analysed in turn. The operating table is situated several metres from the wall-mounted panel in each theatre and so a further 6-m length of 1-mm i.d. polyethylene tubing is used to extend the sampling system to the patient. The final connection is made using a short length (0.1 m) of "Portex" 0.38-mm i.d., 1.0-mm o.d. polyethylene tubing. One end of this is inserted into the open end of the 1-mm i.d. tubing where it makes a leak-free junction of low resistance and without deadspace; the other end is inserted through the rubber suction cap of the endotracheal tube connector.

Calibration procedure

The following routine has proved satisfactory and takes approximately 45 min to complete.

After tuning six or more of the channels to the mass numbers required (usually nitrogen, oxygen, carbon dioxide, nitrous oxide, a volatile agent and argon), those for nitrogen (28), oxygen (32), argon (40) and carbon dioxide (44) are calibrated using known mixtures of these gases (B.O.C. "Hy-line" certified gas mixtures).

The procedure recommended by the manufacturer for erasing overlapping signals is to supply the mass spectrometer in turn with pure nitrous oxide, carbon dioxide and oxygen, and then a mixture of the volatile anaesthetic agent in carbon dioxide. Once the output is stable with each gas (which can take up to 5 min), the unwanted signals are backed off to zero using the appropriate potentiometers. Correction for a volatile agent is only necessary if using concentrations greater than 1%. Once the spectrum overlap eraser circuits have been set, the automatic summing circuit can be operated.

Two modifications have proved necessary in practice. First, pure nitrous oxide is used only to calibrate the upper end of the nitrous oxide scale and to set the spectrum overlap eraser for oxygen; a nitrous oxide mixture is used to set the spectrum overlap eraser circuits for nitrogen and carbon dioxide. This is because the output signal generated by nitrous oxide is not linearly related to the concentration of the gas above approximately 80%. This non-linearity at high concentration is common to several gases and is not an artefact introduced by the spectrum overlap eraser because it is observed even when these circuits are not in use. Non-linearity is discussed in greater detail in a subsequent section, but its presence means that it is preferable to set the back-off voltages at mass numbers 28 and 44 while the mass spectrometer samples a mixture of 50–80% nitrous oxide in oxygen. Inaccuracies in the measurement of nitrous oxide introduced by setting the upper end of the nitrous oxide scale while sampling pure nitrous oxide are regarded as unimportant in clinical practice, and the error on the oxygen scale caused by setting the spectrum overlap eraser for this gas while sampling pure nitrous oxide is trivial because the overlapping signal derived from nitrous oxide at mass 32 is very small.

Second, exposure to air or to pure nitrogen is required so that a back-off voltage can be set to eliminate the signal at mass 30 which reflects the presence of nitrogen-15 in small quantities. The spare potentiometer on the nitrous oxide channel can be used for this purpose. The fact that there is reciprocal overlap between nitrogen and nitrous oxide is unimportant in practice because, although nitrous oxide produces a sizeable peak at mass 28, the signal at mass 30 derived from nitrogen is very small. It cannot be ignored, however, because the gain at mass 30 must be high for adequate detection of the signal from nitrous oxide. The output from nitrous oxide at mass 28 should be eliminated first, therefore, followed by the small signal from nitrogen at mass 30.

The output on all channels should be re-checked in an appropriate gas mixture to detect and adjust for any alteration in sensitivity occurring during the calibration procedure and then the automatic summing circuit can be operated.

EVALUATION OF THE SYSTEM

Linearity

This feature can be evaluated only when the ASC is not in use because the performance of the summing circuit is such that the total signal output is always 100%, each component being adjusted in proportion. Calibration checks were made at from four to eight points using air, or certified gas mixtures in which the concentration of any individual gas did not exceed 80%. The output was linear and accurate to within 1% over the range encountered in clinical practice for all the respiratory gases except oxygen (fig. 1). Linearity of the output of the oxygen channel has been confirmed over the range 0–60%. Falsely low values are recorded when a high concentration (more than 80%) of any gas is supplied, even though the appropriate channel has been calibrated correctly over a lower range. This means that adjustments to the calibration should not be made when a pure gas is sampled to set the spectrum overlap eraser circuits.

Linearity has been difficult to assess for nitrous oxide because certified mixtures are not available, and the tolerance of "Entonox" (50% nitrous oxide in oxygen) is only ±2%. However, evidence suggesting that the response to nitrous oxide is also non-linear can be obtained in the following way. The spectrum overlap eraser circuits for nitrogen and carbon dioxide are set so that the outputs of the respective channels are zero while the mass spectrometer is sampling 100% nitrous oxide. It should be noted that trace amounts of carbon dioxide are generated within the ionizing chamber and are detected as a "zero current" at mass 44 when no carbon dioxide is being supplied to the instrument. The spectrum overlap eraser for carbon dioxide is set to this figure rather than to zero. If the mass spectrometer is then allowed to

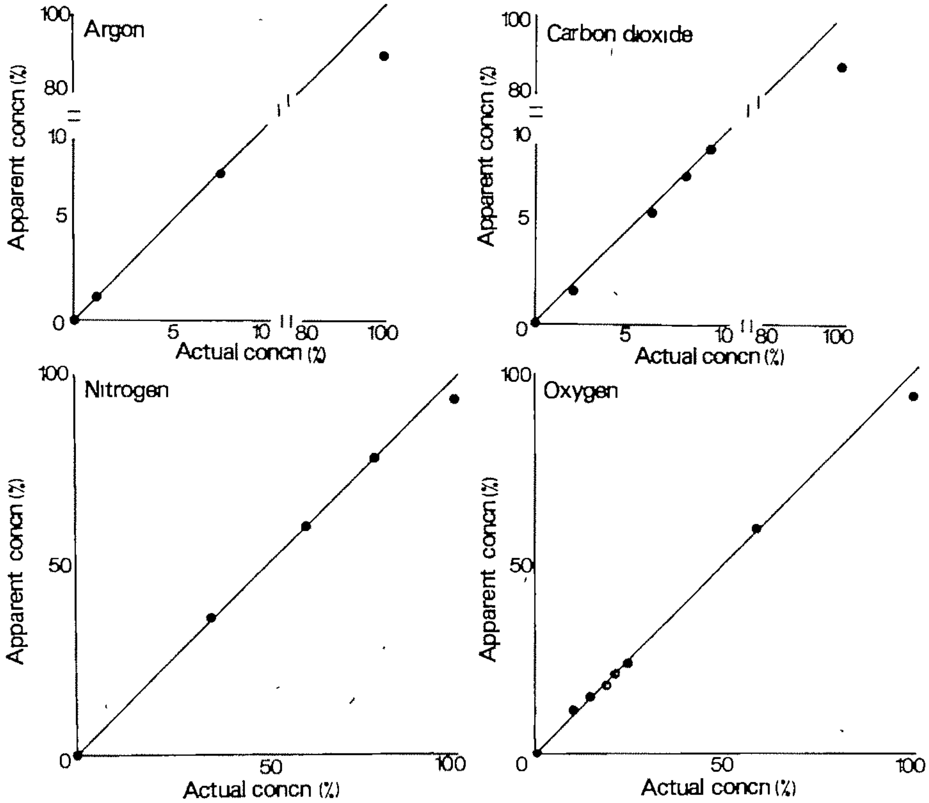

FIG. 1. Plot of apparent against actual concentrations for four different gases. Individual points are plotted against the line of identity.

sample mixtures of nitrous oxide in oxygen, spurious values for carbon dioxide and nitrogen are recorded, those for carbon dioxide being falsely positive and those for nitrogen falsely negative (table I). These findings suggest both non-linearity of the response to nitrous oxide and that the degree of non-linearity for nitrous oxide differs from that of the fractions into which it fragments. It is for this reason that the technique of setting the spectrum overlap eraser circuits for nitrogen and carbon dioxide while sampling 50–80% nitrous oxide in oxygen has been advocated.

TABLE I. *Apparent concentrations of carbon dioxide and nitrogen, recorded in the presence of different concentrations of nitrous oxide, when the spectrum overlap eraser circuits for carbon dioxide and nitrogen had been set while the mass spectrometer sampled 100% nitrous oxide. Approximate concentrations of nitrous oxide (in oxygen) were supplied from a Boyle's apparatus*

Nitrous oxide (%)	Carbon dioxide (apparent %)	Nitrogen (apparent %)
100	0.1	0.0
Approx. 80	1.25	−0.6
Approx. 67	1.1	−0.4
Approx. 50	1.1	−0.5

The delivery of a pure gas to the mass spectrometer causes a distortion of the readings on all channels when a mixture of gases is sampled subsequently. This distortion lasts for up to 5 min and the direction of the error depends on the nature of the preceding gas: 100% oxygen augments all readings by approximately 10% whereas 100% nitrogen depresses them by 5%. Depression followed by an overswing is seen after pure argon, whereas previous exposure to pure carbon dioxide depresses the readings of all gases in a mixture, except for carbon dioxide itself, which is augmented. These observations are, of course, modified if the ASC is in use because then the total signal output is always adjusted to 100%.

The explanation for this effect of pure gas is unknown, but it could be caused by loose combination with or solution in the ionizer filament or the metal of the electron multiplier. It cannot be ignored entirely during anaesthesia because high concentrations of oxygen, up to and including 100%, are used in some circumstances. The effect of pure oxygen is to augment the output from all channels to approximately the same extent and so operation of the automatic summing circuit adjusts each signal in proportion. However, all measurements made in the presence of high concentrations of oxygen (more than 80%) should be viewed with caution because of the non-linearity of the output towards the upper end of the range.

Stability

Recalibration at intervals confirmed that the output signals for nitrogen, oxygen and argon altered by less than 1% of full-scale deflection in 24 h if the instrument was operated with the ASC. Values for carbon dioxide were equally stable in the absence of nitrous oxide, but zero concentrations of carbon dioxide registered up to ±2% after 24 h if the instrument sampled high concentrations of nitrous oxide; the signal for nitrous oxide changed by up to 1% full scale deflection at the same time. This greater inaccuracy at mass 44 in the presence of nitrous oxide was attributed to summation of drift on both the nitrous oxide and carbon dioxide channels.

The spectrum overlap eraser potentiometers required adjustment by less than 1% of each setting in 24 h, and the settings of the mass tuning potentiometers were stable to within 0.1% over 48 h.

Response times and sampling rate

When a new gas mixture is presented to the tip of a long sampling probe, there is a delay before the change is detected. The transit time is the time taken for the sample to traverse the long probe; the response time is the interval required for the mass spectrometer to register the change, starting from the instant that the signal begins to alter.

These intervals have been measured for various gases and different assemblies of tubing. The tip of the probe was removed swiftly from the test gas and the transit time was measured with a stop watch. Once the transit time had been established, the response time was determined by freezing the signal on a storage oscilloscope (sweep time 500 or 1000 ms), photographing the trace and measuring the 0–95% change. The sampling rate of the system was measured by timing the clearance of a known volume of gas from a collapsible container (a rubber glove).

Transit times, response times and sampling rates for a variety of probes and gases are shown in table II. A long length of fine tubing between the patient and the wall-mounted connector proved impractical because the sampling rate and response times were too slow. A short length of fine

TABLE II *Sampling rates, transit times and response times for various gases and probe assemblies. Each measurement was made in duplicate. The coefficient of variation determined on eight measurements using one probe in one gas was 3.1%.*CO_2: a mixture of 8% carbon dioxide in 60% nitrogen, 24% oxygen and 8% argon*

Probe assembly	Sampling rate (ml min^{-1})	Transit time (s)	Response time (ms)	Gas
25 m × 1.0-mm i.d. polyethylene		5.5	205	Ar
			280	CO_2
25 m × 1.0 mm polyethylene + wall connector		5.6		
25 m × 1.0 mm polyethylene + wall connector		8.0	265	Ar
+6 m × 1.0-mm i.d polyethylene			455	CO_2
25 m × 1.0 mm polyeth. + connector + 6 m × 1.0 mm polyeth				
+0.5 m × 0.38-mm i.d. polyethylene	72	10.9	620	CO_2
			615	*CO_2
+0.75 m × 0.38 mm polyethylene	55	12.0	795	CO_2
+1.25 m × 0.38 mm polyethylene	42	13.9	860	CO_2
+0.1 m × 0.38 mm polyethylene	112	8.5	205	Ar
			425	CO_2
			90	He
			175	SF_6
15 m × 1.0 mm polyeth. + connector + 6 m × 1.0 mm polyeth.				
+0.5 m × 0.38 mm polyethylene	85	5.7	430	CO_2
+0.1 m × 0.38 mm polyethylene	131	5.3	185	Ar
			265	CO_2
			350	N_2O
			200	O_2
			79	He
			175	SF_6
25 m × 1.0 mm polyeth. + connector + 6 m × 1.0-mm i.d. nylon				
+1.0 m × 0.25-mm i.d. nylon	23	18.8	1075	CO_2
+0.5 m × 0.25-mm i.d. nylon	40	14.1	365	Ar
			720	CO_2

tubing is desirable, however, to concentrate the resistance of the sampling probe at the tip (Glaister and Farncombe, 1979), to act as a filter, and to achieve an adequate but not excessive sampling rate. A 0–95% response time of less than 500 ms is achieved for all gases if the end of the probe is 0.1 m of 0.38-mm i.d. polyethylene tubing. Polyethylene rather than nylon tubing was chosen to minimize uptake of water vapour which, it was thought, might absorb and subsequently release soluble gases, so interfering with the composition of the sample. This hypothetical advantage has since been disproved because polyethylene itself can absorb a number of gases, the solubility of some at least being similar to their solubility in water (table III). Polyethylene, however, is easy to handle, does not kink readily, and a satisfactory junction can be made very easily between the short length of fine tubing at the tip and the wider bore tubing which forms the major part of the probe.

Considerable disparity was noted between the response times for different gases (table II). Goodwin (1979) related response time to viscosity when sampling with a probe of narrow and uniform bore, but a more complex relationship exists when the diameter of the probe is not constant (Glaister and Farncombe, 1979). A Spearman rank correlation test suggests that the response time may have some relation to solubility in water (and hence probably to solubility in polyethylene), possibly to viscosity, but not to molecular weight (table III). It seems likely, therefore, that uptake of gases within the probe and probably viscosity of the sample are the factors responsible for the different response times.

A further observation which supports the view that soluble gases are absorbed by the walls of the tubing is that the response time for nitrous oxide depends on whether the sampling probe has recently been exposed to the gas. Thus, the rise time

TABLE III. *Response times of a variety of gases sampled through the same probe assembly (15 m × 1.0 mm polyethylene + wall connector + 6 m × 1.0 mm polyethylene + 0.1 m × 0.38 mm polyethylene) and compared with their viscosities, molecular weight and solubilities in water and polyethylene. *Solubility of gases in water expressed as Bunsen coefficient (vol. s.t.p.d. vol^{-1} atm^{-1}) in water at 20 °C (Kaye and Laby, 1966; British Oxygen Co., Special Gases Division, personal communication). Solubility in polyethylene expressed as ml at s.t.p./ml polyethylene atm^{-1} (Imperial Chemical Industries, Plastics Division, personal communication)*

Gas	Mol. weight	Solubility*		Viscosity (Nsm^{-2} × 10^{-7})	Response time (ms)
		Water	Polyethylene		
N_2O	44	0.63	—	146	350
CO_2	44	0.85	0.25	146	265
O_2	32	0.03	0.04	200	200
Ar	40	0.032	—	222	185
SF_6	146	0.001	—	148	175
He	4	0.0086	0.006	186	79
Spearman correl. coeff.	0.1714	0.8286	—	0.5143	

of a previously unused probe, measured as soon as it is exposed to nitrous oxide, is very slow (approximately 5 s). A probe which has been left full of nitrous oxide for some hours or which has been used recently to sample a nitrous oxide-containing gas mixture has a response time of 300–500 ms.

The validity of physiological signals recorded through long sampling probes has been explored by Davies and Denison (1979). They reported response times of 200–300 ms for helium and sulphur hexafluoride, values similar to those determined for these gases in the present study. Although the response times for carbon dioxide and nitrous oxide are considerably longer, the accuracy with which carbon dioxide waveforms could be recorded through the comparable probe assembly used by Davies and Denison (1979), suggests that remote monitoring during anaesthesia will be adequate for all but the fastest respiratory events, for example a spontaneously breathing infant.

CONCLUSION

It can be concluded that the stability, linearity and response times of the system reported here are satisfactory for monitoring respiratory gases during anaesthesia. Accurate measurement is possible only when the inspired concentration of each gas is less than 80%. Allowance for the non-linearity of response to nitrous oxide should be made by setting the spectrum overlap eraser circuits for nitrogen and carbon dioxide while the mass spectrometer samples a 50–80% mixture of nitrous oxide in oxygen, rather than the pure gas. Recalibration of the carbon dioxide channel is required at least every 8 h; this means attention from an operator familiar with the apparatus, which places some constraint upon the routine use of the system.

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SPECTROMETRIE DE MASSE RESPIRATOIRE PENDANT L'ANESTHESIE GENERALE

RESUME

On a procédé à l'évaluation des performances d'un spectromètre de masse respiratoire, modifié dans le commerce, pour utilisation pendant l'anesthésie générale. Sa stabilité et sa linéarité ont été jugées satisfaisantes pour la surveillance des gaz respiratoires et on a pu prendre des mesures précises lorsque la concentration inspirée de tous les gaz a été inférieure à 80%. Le systéme a été installé au centre d'une salle d'opérations comportant trois pièces et on discute dans cet article du choix des longues sondes d'échantillonnage qui permettent d'obtenir un temps de réponse adéquat pour tous les gaz.

RESPIRATORISCHE MASSENSPEKTROMETRIE UNTER ALLGEMEINER NARKOSE

ZUSAMMENFASSUNG

Die Leistung eines respiratorischen Massenspektrometers, kommerziell modifiziert zur Verwendung während allgemeiner Narkose, wurde untersucht. Stabilitat und Linearitat erwiesen sich als zufriedenstellend fur die Bestimmung von Atmungsgasen, und eine genaue Messung war möglich, wenn die eingeatmete Konzentration aller Gase weniger als 80% betrug. Das System war zentral in einer Suite von drei Operationssalen installiert worden, und diskutiert wird die Auswahl langer Gasproben, die eine adaquate Reaktionszeit für alle Gase gestatten.

ESPECTROMETRÍA RESPIRATORIA DE MASAS DURANTE ANESTESIA GENERAL

SUMARIO

Se evaluó el rendimiento de un espectrómetro de masas para respiración, modificado comercialmente para usarse durante la anestesia general. La estabilidad y la linearidad mostraron ser satisfactorias en lo tocante a gases respiratorios de control y fue posible la precisa medición cuando la concentración de todos los gases aspirados fue inferior al 80%. El sistema se ha instalado con carácter central en un teatro de operaciones de tres salas y, asimismo, se discute la selección de largas sondas de muestreo que permitan un adecuado tiempo de respuesta para todos los gases.

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EFFECTS OF HALOTHANE AND ENFLURANE ON MYOCARDIUM SUPPLIED BY A NARROWED CORONARY ARTERY

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Most of the experimental studies of the effects of anaesthesia on the myocardium have been carried out on normal hearts. Only a few studies have examined regional myocardial function in animals with acute myocardial ischaemia. Bland and Lowenstein (1976) have shown that halothane minimizes the severity of ST segment elevation as a result of acute coronary occlusion. Smith, Rogers and Thorburn (1980) have shown that halothane improves the balance of oxygen supply to demand of ischaemic myocardium suggesting that halothane may protect the myocardium.

Studies of the effects of anaesthesia on cardiac performance when a coronary artery is narrowed may be more clinically relevant than studies carried out when a coronary artery is occluded.

Regional myocardial function may be evaluated by measuring segment length continuously with subendocardial ultrasonic transducers. Global cardiac function may be evaluated by recording e.c.g., aortic, ventricular and left atrial pressures, aortic blood flow and LV dP/dt max.

We have studied the effects of halothane and enflurane on regional and global cardiac function before and after critical constriction of the left anterior descending coronary artery (LAD). Critical constriction was defined as the maximum amount of tightening of a micrometer-controlled snare placed around the LAD that is compatible with normal regional contraction and abolishes the hyperaemic response to a 10-s occlusion of the vessel.

In eight dogs the effects of stepwise increases of halothane concentration (0.5% to 2%) were studied. Dose-dependent reductions of mean arterial pressure (up to 39%), of LV dP/dt_{max} (up to 50%), of aortic blood acceleration (up to 58%), of cardiac output (up to 38%) and of shortening (up to 23% for the LAD segment and up to 20% for the control segment) were observed before critical constriction of LAD. After critical constriction, the dose-dependent effects of halothane on global function were similar to those observed before constriction. However, the LAD segment showed greater depression of shortening (up to 54%), whilst the control segment behaved as before. Paradoxical systolic lengthening and post-systolic shortening were observed.

In eight dogs, the effects of stepwise increases of enflurane concentration (1.1 to 3.3%) were studied. Dose dependent reductions of mean arterial pressure (up to 32%), of LV dP/dt_{max} (up to 50%), of cardiac output (up to 38%), and of shortening (up to 41% in the LAD segment and up to 30% in the control segment) were observed. After critical constriction of LAD, the dose-related reductions of mean arterial pressure (up to 44%), of LV dP/dt_{max} (up to 57%) and of cardiac output (up to 54%) were greater than before critical constriction. The dose-related reductions of shortening were more pronounced (up to 53%) in the LAD segment and less pronounced (up to 25%) in the control segment than before critical constriction.

In the case of a critically narrowed coronary artery, halothane and enflurane impair regional performance more than global performance. Paradoxical wall motion may occur and may cause wall stresses. Such stresses may contribute to the cardiac risks of anaesthesia.

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NALOXONE IN THE TREATMENT OF ENDOTOXIN SHOCK

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In 15 mongrel dogs, anaesthetized and the lungs ventilated artificially, the effect of pretreatment with naloxone 10 mg kg^{-1} i.v. on the cardiovascular effects of a subsequent dose of 6 mg kg^{-1} of endotoxin was investigated. Compared with the controls naloxone prevented or reduced the depressant effects of a high dose of endotoxin (table I). The naloxone-pretreated animals showed either no change or a less marked reduction in mean aortic pressure (MAP), cardiac index (CI), stroke volume index, maximum dp/dt, left ventricular work, coronary blood flow (MBF), myocardial oxygen consumption and efficiency of left ventricular work (EME). The naloxone

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TABLE I. *Mean changes after endotoxin 6.0 mg kg^{-1} i.v. C = control* (n = *8*), *N = naloxone* (n = *7*) $^*2P<0.05$

	Mean aortic pressure (mm Hg)		Cardiac index (ml·kg^{-1} min)		Max dp/dt (mm Hg s^{-1})		Coronary flow (ml min^{-1} per 100 g)		Efficiency L.V. work (%)	
	C	N	C	N	C	N	C	N	C	N
Control	124.5	126.6	114.5	99.1	1583	2327	73 1	64.1	22.3	17.1
10 min	−44.6*	−4.4	−45.7	*0.4	−803*	288	−29.7*	−1.2	−7.7*	2.4
30 min	−41.5*	−7.1	−24.8*	13.8	−593*	442	−18.2	−3.6	−4.1	3.1
60 min	−56.6*	−28.3	−37.8*	−0.8	−723*	76	−26.8	−11.0	−7.2	−0.3
90 min	−60.6	−39.7	−42.3*	−18.3	−778*	−234	−23.1	−9.0	−9.0	−4.2
120 min	−59.1	−38.3	−49.4*	−23.8	−784*	−240	−26.2	−10.1	−8.9	−3.4
180 min	−50.3	−38.8	−52.1*	−24.3	−688	−216	−27.7	−10.9	−9.9	−3.7

effect waned 60 min after endotoxin injection. Clinical implications for the use of naloxone in the therapy of shock will be discussed.

EFFECTS OF VARIOUS ANAESTHETICS ON HAEMODYNAMICS AND RENAL BLOOD FLOW

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Mean aortic pressure (MAP), cardiac output (CO), renal blood flow (RBF) and plasma renin activity (PRA) were studied in dogs receiving various i.v. anaesthetics and under either extradural block or light halothane nitrous oxide in oxygen anaesthesia, the latter serving as control. Under steady state conditions autoregulation of RBF and the fraction of RBF on CO were investigated in detail (table I).

With thiopentone, Althesin and propanidid in clinical doses autoregulation was maintained. Ketamine shifted the autoregulation plateau slightly upwards, whereas etomidate produced a significant decrease. During halothane anaesthesia renal blood flow (RBF) reflected cardiac output (CO) when the latter was normal or reduced, but was unchanged when cardiac output was increased (greater than 150 ml min^{-1} kg^{-1}). With Althesin, RBF and CO were essentially unchanged. Thiopentone with and without halothane produced a varying haemodynamic state, but the relationship between RBF and CO was maintained. With ketamine regulation of renal circulation was similar to that obtained under conditions of high cardiac output. Etomidate reduced RBF and CO to the same extent because of an increase in renal and general vascular resistance.

Propanidid in combination with halothane produced variations in renal circulation similar to those in patients with heart failure: CO was maintained but renal perfusion diminished. After halothane was withdrawn general haemodynamics under propanidid showed reactions comparable to a histamine effect with an increase in CO, while RBF was unaffected.

Under fentanyl, RBF and CO decreased to the same extent without significant changes in MAP. Atropine, droperidol and extradural block (T7) abolished the response of CO and RBF to fentanyl. The renin–angiotensin response to changes in arterial presssure produced by the i.v. anaesthetics appears to be a major homeostatic mechanism in view of a reduced catecholamine liberation during halothane anaesthesia. It was observed further, that all variations in RBF produced by the anaesthetics were secondary to changes in the general circulation. Specific anaesthetic action on renal function is (if present at all) of minor importance.

FAILURE OF EXTRADURAL MORPHINE TO PROVIDE ADEQUATE PAIN RELIEF IN LABOUR

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After giving informed consent, 30 women in labour received either 5 mg of morphine hydrochloride in 10 ml of normal

TABLE I. *Effects of i.v. anaesthetics in nitrous oxide in oxygen analgesia* (*IVA*) *compared with light halothane* (<0.7 *vol%*)*–nitrous oxide and oxygen anaesthesia* (*HA*). *Extradural block effects are presented during HA.* $^*2P<0.05$

		MAP (mm Hg)		CO (ml min^{-1} kg^{-1})		RBF (ml min^{-1} dl^{-1})		PRA (ng ml^{-1} h^{-1})	
Anaesthetic	*n*	HA	IVA	HA	IVA	HA	IVA	HA	IVA
Ketamine 4 mg h^{-1} kg^{-1}	10	108	136*	133	167*	319	355*	10.7	9.0
Thiopentone 10 mg h^{-1} kg^{-1}	7	109	131*	132	142	304	311	8 4	14.4
Etomidate 1 mg h^{-1} kg^{-1}	7	109	128*	116	101*	296	240*	12.1	16.2
Propanidid 35 mg h^{-1} kg^{-1}	10	111	117	137	153	334	322	11 9	64.5*
Althesin 0.67 ml h^{-1} kg^{-1}	5	116	103	135	141	330	318	9.0	12.4
Fentanyl 0.05 mg h^{-1} kg^{-1}	14	117	111	129	90*	343	228*	15.2	36.8*
EB (mepivacaine 2%) 8 ml	6	113	93*	139	140	345	337*	12.4	13.8

saline or saline alone by an extradural catheter in a double-blind randomized study.

The extradural catheter was inserted at the L2–L3 or L3–L4 interspace when contractions had become well established and cervical dilatation had reached 2–3 cm.

Uterine activity, maternal arterial pressure and respiration were closely monitored and constant attention given to possible side-effects of morphine (nausea, vomiting, itching). Fetal heart rate was recorded continuously.

Pain was rated by the parturient as 0 = no pain, 1 = slight pain, 2 = severe, and 3 = unbearable. A rating was established before the injection and 30 min afterwards. If no pain relief had been obtained at the time of the second rating, 0.375% bupivacaine 8–12 ml was injected via the extradural catheter. Top-up injections were given when needed.

If some relief had been obtained, injection of bupivacaine was deferred until the time the patient asked for pain relief. Five in the morphine group and three in the saline group did not require any bupivacaine.

There were five cases of incomplete records or unforeseen changes. Of the remaining 25, morphine had been administered in 13, saline in 12. There were 10 primiparae and three multiparae in the morphine group and nine primiparae and three multiparae in the saline group. Mean pre-injection pain rating was 2.38 in the morphine group and 2.35 in the saline group. Mean pain reduction was 0.63 at the second rating 30 min later in the morphine group and 0.21 in the saline group. A reduction of pain intensity of 0.5 points or more was obtained in eight of the 13 receiving morphine and five of the 12 receiving saline. The total volume of 0.375% bupivacaine given until birth to achieve pain relief was 14.38 ± 4.43 ml in the morphine group and 10.77 ± 3.93 ml in the saline group. Neither of these differences is statistically significant at the 0.05 level.

In one of the patients receiving morphine, severe itching occurred 5 h after the injection. In one who received saline, hypotension occurred after 10 ml of 0.375% bupivacaine.

Apgar scores of 7 or less were found at 1 min in one patient in the morphine group (after instrumental extraction for dystocia) and one in the saline group in which Caesarean section had been performed. The scores were 9 and 10 respectively at the 10th min.

Neurosensory testing according to the method of Amiel–Barrier–Shnider at the 30th min of life gave a total of 27/30 in all cases.

While no major side-effects occurred, extradural morphine failed to provide adequate pain relief in the study.

OBSTETRIC ANALGESIA WITH FENTANYL ADMINISTERED BY THE EXTRADURAL ROUTE

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Following our experience of extradural administration of morphine to patients with acute or chronic pain, we have given fentanyl by the extradural route for analgesia in labour. We report preliminary results in an unselected group of 30 patients, mean age 25.4 yr, mean weight 52 kg, with normal term pregnancy.

In all patients the extradural space was entered at L1–L2, leaving a catheter directed 3 cm downwards, through which fentanyl 0.005 mg kg^{-1} was given when cervical dilatation reached 4 cm.

In all the patients we monitored lung ventilation, arterial pressure, heart rate, fetal heart rate and uterine activity, together with periodic blood sampling for maternal and fetal acid–base assessment.

We obtained excellent results in 28 cases. There was no case of fetal or maternal depression, no adverse effect on uterine activity, and no abnormality in the follow-up assessment of the newborn of mothers receiving fentanyl by the extradural route.

A NEW APPROACH TO ARTIFICIAL EXPANSION AND VENTILATION OF THE LUNG IN THE SEVERELY ASPHYXIATED NEONATE

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When there is severe asphyxia resulting in birth apnoea, expansion of the newborn lung must precede ventilation by intermittent positive pressure. The applied pressure may be insufficient to cause full expansion with resultant hypoxia or may cause over-expansion and rupture of the lung. The only way in which a pre-determined pressure can be achieved, and not exceeded in the alveoli, is to apply that pressure at the upper end of the airway (the mouth) and to wait until all flow ceases. Applying pressure in this way and increasing it in steps of suitable size at selected intervals should ensure that the maximum pressure produced in the alveoli is the minimum necessary for resuscitating each infant. On the basis of work in this Department, ranges of optimum values for the initial pressure (1.5–2 kPa), increments (0.25–1 kPa) and time intervals (5–30 s), are suggested. Clinical judgement is still necessary to select from within these ranges, but this "pressure staircase" method provides a systematic approach A suitable apparatus is described which avoids short-term high pressure (waterhammer effect) and the pressure settings are each virtually independent of flow up to 50 litre min^{-1}.

EXPERIMENTAL STUDIES ON THE EFFECTS OF PEEP AND DIFFERENT VENTILATION–COMPRESSION RATIOS IN NEONATAL CARDIOPULMONARY RESUSCITATION

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In both animals and man it has been demonstrated that during cardiopulmonary resuscitation the intrapulmonary shunt may be about 50% of the cardiac output or even more. Ventilation–compression ratios of 1 : 5 are still recommended for neonatal cardiopulmonary resuscitation.

To study the effects of ventilation with PEEP and of different ventilation–compression ratios during cardiopulmonary resuscitation, 36 pigs (mean body weight 4–5 kg) were anaesthetized, the trachea intubated and the lungs artificially ventilated. After catheters were placed in the internal jugular vein and the carotid artery, cardiac arrest was initiated by administering potassium chloride i.v.

Immediately after, cardiopulmonary resuscitation was started using ventilation rates of either 30 or 40 b.p.m. and compression rates of 60, 80–100, 120 or 160 per min. Each of the 36 animals received ventilation–compression ratios of 1 : 2, 1 : 3 and 1 : 4 Finally, within two groups the effects of either 5 cm or 0 cm end-expiratory pressure were compared.

The systolic arterial pressure decreased with increasing compression rates and with increasing ventilation rates. Diastolic arterial pressure decreased to almost 5 mm Hg, the mean arterial pressures within all groups being about 25 mm Hg after 5 min and a little less than 25 mm Hg after 10 min.

Blood-gas tension measurement did not show any difference which can be related to the ventilation–compression ratios. A significant increase in arterial $P\text{O}_2$ was observed with respiratory rates of 40 compared with 30 b.p.m.

Using carbon dioxide elimination as an indicator of successful resuscitation, the respiratory rate of 40 b.p.m. and ventilation–compression ratios of 1 : 3 instead of 1 : 4 or 1 : 5 should be preferred. Oxygenation can be significantly improved by the immediate application of 5 cm H_2O PEEP.

EFFECT OF DOBUTAMINE ON BLOOD FLOW THROUGH COLLAPSED LUNG

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Regional alveolar hypoxia produced by ventilation of a lung or lobe with hypoxic gas mixtures causes pulmonary vasoconstriction. This reduces the blood-flow to the hypoxic area and so minimizes the decrease in arterial $P\text{O}_2$. It has now been shown that dobutamine and a number of inotropic, bronchodilator and inhalation anaesthetic drugs may reversibly inhibit the hypoxic pulmonary vasoconstrictor mechanism, thus increasing the blood flow to the hypoxic areas of lung so that there is a further decrease in arterial $P\text{O}_2$. The purpose of the present experiments was to determine whether dobutamine could increase shunt by inhibiting pulmonary vasoconstriction in a collapsed left lower lobe of the dog.

Seven dogs were anaesthetized with thiopentone and pentobarbitone, and the lungs ventilated mechanically with 100% oxygen. A left thoracotomy was performed and an electromagnetic flow-probe placed around the left lower lobe pulmonary artery. The lobe was ventilated independently with 100% oxygen Dobutamine $30\ \mu g\ kg^{-1}\ min^{-1}$ was administered i.v.: (a) during ventilation of the lobe with 7% oxygen in nitrogen; (b) during collapse produced by occlusion of the endobronchial tube after the lobe had been ventilated with 100% oxygen for at least 30 min; (c) after re-expansion of the lobe and a second period of ventilation with 7% oxygen in nitrogen Cardiac output was determined by the dye dilution method and the flow to the lobe expressed as a percentage of the total blood flow ($\dot{Q}_L/\dot{Q}_T$) Catheters were also inserted for measurement of aortic and pulmonary arterial pressures.

$\dot{Q}_L/\dot{Q}_T$ decreased during ventilation hypoxia and was reduced further during collapse. During the administration of dobutamine Q_L/Q_T increased significantly during collapse but not during the two periods of ventilation hypoxia. However, dobutamine increased cardiac output and mixed venous $P\text{O}_2$ so that the resultant changes in arterial $P\text{O}_2$ were small. Since there were no significant changes in pulmonary artery or pulmonary artery wedge pressures throughout the experiment, it is concluded that dobutamine may increase flow to a collapsed lung lobe by inhibiting hypoxic pulmonary vasoconstriction.

SOME ASPECT OF MECHANICAL VENTILATION IN INFANTS: A NEW CONCEPT OF WEANING

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In patients with respiratory failure the chief objective of mechanical ventilation is restoration of normal alveolar ventilation. However, most ventilators are not effective in the neonate and there is a particular problem when the infant is being "weaned" from the ventilator. It is known from clinical observation that an infant attempting to overcome lung collapse and to restore FRC exhibits rapid shallow breathing, with exhalation through a partially closed glottis.

In our department, high frequency mechanical ventilation has been introduced. For this purpose our ventilator (RELOG-Inf. G–19, Farum, Warsaw, Poland) has been modified. Time preset constant-flow inspiration, in addition to independent settings for respiratory frequency and I/E ratio, permit continuous measurement of expiratory volume (this is impossible when a constant-flow generator is used in other types of ventilator). The respiratory frequency can vary up to 120 b.p.m. with preset $\dot{V}_E$, V_T and oxygen concentration calculated from simple nomograms; PEEP can be added.

The results of our experimental studies show that adequate alveolar ventilation can be obtained at high ventilatory frequencies, but with advantages of low intratracheal and intrapleural pressures. Application of PEEP (5 cm H_2O) even during ventilation of 100 b.p.m. increased FRC by 25% of the normal value. It was observed that under fast mechanical ventilation V_D/V_T increased significantly with respiratory rate, but alveolar ventilation could be corrected by suitable choice of minute ventilation.

For weaning from the ventilator a new paediatric system of minute mandatory ventilation (PSMMV) is introduced. A double-ended bag-in-box, on the inspiratory line, with two one-way valves has been used. The bag is open to the box for constant calibrated out-flow. The bag, as the indicator of expired volume, is filled according to the regulated and predicted expired minute volume. When the bag is not filled sufficiently, active insufflation of the lung is effected by the ventilator. The pre-set volume (time of constant-flow of gas during inspiratory phase) is sufficient to maintain alveolar ventilation.

A NEW ANAESTHETIC BREATHING SYSTEM

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The principles of a new anaesthetic breathing system are described. The system differs from existing ones in the following important respects:

Without altering the arrangement of components it functions as a closed, semi-closed or non-rebreathing circuit, determined by the fresh gas supply flow only.

No adjustment of the exhaust valve is required, for example when changing from spontaneous to controlled ventilation, or when changing the inflow rate.

Pressures which might damage the lung tissue cannot occur no matter how great the inflow of fresh gas.

Alveolar air is always exhausted from the system in preference to fresh gas, thus ensuring maximum fresh gas economy.

FACTORS AFFECTING THE PERFORMANCE OF CIRCLE SYSTEMS USED WITHOUT CARBON DIOXIDE ABSORPTION

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A circle system with an attached ventilator has been used to ventilate a model lung. The reservoir bag of the system was replaced by a length of corrugated tubing attached to the ventilator outlet. A small constant flow of carbon dioxide entered the lung and tidal carbon dioxide concentrations were measured at various combinations of fresh gas flow ($V\mathrm{F}$), tidal volume ($V\mathrm{T}$), and respiratory frequency (f). Two separate forms of circle geometry were studied.

A greater efficiency—that is a lower end-tidal carbon dioxide ($F\acute{E}_{CO_2}$) at any given value of $V\mathrm{F}$ and $V\mathrm{E}$—was found when fresh gas entered the system on the lung side as opposed to the ventilator side of the unidirectional inspiratory valve. This was ascribed to the former arrangement having a greater capacity to store fresh gas in the inspiratory limb, and is in agreement with the findings of Snowdon and others (1975). With the latter form of fresh gas entry used at a constant respiratory frequency, multinomial regression equations relating $F\acute{E}_{CO_2}$ to $V\mathrm{F}$ and $V\mathrm{E}$ had correlation coefficients which approached unity. Increasing f reduced efficiency. Poor relationships were found between $F\acute{E}_{CO_2}$, $V\mathrm{F}$ and $V\mathrm{E}$ when $V\mathrm{T}$ was kept constant and $V\mathrm{E}$ varied by varying frequency. These differences in behaviour appear to be a result of gas mixing within the system being greatly affected by changes in frequency. As frequency increases fresh and expired gas in the system become more uniformly mixed.

Inconsistent and non-reproducible results were obtained when a bag-in-box arrangement was used to ventilate the system and gas was vented from the system during inspiration. Under these circumstances behaviour of the system was greatly influenced by any changes in the resistance of the pop-off valve and by any changes in the dynamics of the system.

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PHARMACOKINETICS OF CONTINUOUS INFUSIONS OF ALTHESIN, MINAXOLONE AND ICI 35 868 TO SUPPLEMENT NITROUS OXIDE ANAESTHESIA IN MAN

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The steroid anaesthetics, Althesin or minaxolone (a new water soluble steroid), or ICI 35 868 (di-isopropyl phenol) have been administered as continuous i.v. infusions to supplement nitrous oxide 67% in oxygen anaesthesia. We have defined the minimum infusion rate (MIR) for i.v. agents as that infusion rate which suppressed movement of the patient in response to the initial and to subsequent sustained surgical stimulation. Following premedication with morphine 0 15 mg kg^{-1} and atropine 0.6 mg, MIR for 11 patients receiving Althesin was 18.0 ± 0.9 (SEM) μg min^{-1} kg^{-1} as total steroid, equivalent to 13.5 ± 0.7 μg min^{-1} kg^{-1} as alphaxalone. For nine patients receiving minaxolone MIR was 11.0 ± 0 5 μg min^{-1} kg^{-1}, and for eight patients receiving ICI 35 868 51.3 ± 3.8 μg min^{-1} kg^{-1}. There was no evidence of accumulation of any of the three drugs as the plasma concentrations remained steady between 30 min after starting the infusion, and the end of the infusion (range 55–245 min after the start) At the minimum infusion rates quoted above the plasma concentrations of the three i.v. agents were: alphaxalone 1.9 ± 0.1 μg ml^{-1}; minaxolone 0.6 ± 0.05 μg ml^{-1}, ICI 35 868 1.54 ± 0.22 μg ml^{-1}.

Following cessation of the infusions the plasma concentrations of the drugs decayed exponentially with time and could best be fitted to two-compartment models (alphaxalone, ICI 35 868) or three-compartment kinetic models (minaxolone). Recovery of consciousness, assessed by the time from end of infusion to opening the eyes to command (t_1) or to recalling the date of birth (t_2) was particularly rapid following infusions of ICI 35 868 ($t_1 = 5.0 \pm 0.3$ min; $t_2 = 6.9 \pm 0.4$ min), and delayed after minaxolone ($t_1 = 34.0 \pm 8\ 0$ min) and Althesin ($t_1 = 26.0 \pm 3.0$ min).

These findings can only partly be explained in relation to the plasma concentrations of the drugs, and account must be taken of the clearance of the drug from the c n.s rather than from the plasma. In this respect the fat-soluble drugs Althesin and ICI 35 868 appear to have marked advantages over the water soluble minaxolone. No adverse sequelae have been observed following continuous infusions of ICI 35 868 to supplement nitrous oxide anaesthesia.

EFFECTS OF PREMEDICATION AND SPEED OF INJECTION ON INDUCTION OF ANAESTHESIA WITH ICI 35 868

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The clinical usefulness of ICI 35 868 (2,6-di-isopropylphenol) as anaesthetic induction agent was examined in a previous study (Rolly, Versichelen and Zubair, in preparation). A dose of 1.5 mg kg^{-1} was found most convenient in 39 non-premedicated patients. In the present study the usefulness of premedication with fentanyl 0.1 mg (F) or without (S = saline) and the speed of i v injection (10 or 20 s) of 1.5 mg kg^{-1} of a 1% ICI 35 868 solution in 16% Cremophor with water to 100% given in a fast running saline drip were assessed A total of 32 ASA I patients was assigned by randomization to four equal groups: F_{10}, F_{20}, S_{10}, S_{20}. The induction time, absence of eyelash reflex and response to painful stimulus 1 min after start of injection were assessed. Respiratory rate, arterial pressure and heart rate were recorded before, and 1, 2 and 3 min after injection. Eventual side-effects were assessed

Induction times were: F_{10}: 39.4±8.9 (SEM) s; F_{20}. 45.4±2.4; S_{10}: 36.6±4.7, S_{20}: 44.4±3.1. Eyelash reflex was not abolished in 12 patients. Response to painful stimulus was absent in three, slight in 19 and gross in 10 of the 32 patients. In all but the S_{20} group systolic arterial pressure decreased significantly. Heart rate decrease was not statistically significant in any group. Respiratory rate decreased significantly at 1 min in groups F_{20}, S_{10} and S_{20}, but more in groups S_{10} and S_{20} (difference statistically significant).

Gross limb movement occurred after injection in two patients (1 S_{10} and 1 F_{10}) and coughing in three patients. Pain was noticed during injection in four patients (two mild, one moderate and one severe). Vein palpation was painful the next day in five patients.

EFFECT OF HYPO- OR HYPERCARBIA ON THE NEOSTIGMINE ANTAGONISM OF PANCURONIUM-INDUCED NEUROMUSCULAR BLOCKADE IN MAN

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Hypercarbia is known to attenuate the twitch response to nerve stimulation during a tubocurarine block (Katz and Wolf, 1964). Respiratory acidosis has been shown to prevent complete antagonism of tubocurarine and pancuronium (Pc) block by neostigmine in cats (Miller et al., 1975; Miller and Roderick, 1978). We have studied the influence of moderate hypo- or hypercarbia, as occurs in clinical practice, on neostigmine antagonism of Pc-induced neuromuscular blockade in man. Twenty-one patients undergoing elective surgery lasting about 1 h were matched in three groups of seven patients. After induction with thiopentone, intubation of the trachea was facilitated with suxamethonium 0.7 mg kg^{-1}. Nitrous oxide in oxygen and fentanyl were given for maintenance of anaesthesia and about 90% twitch suppression of thumb adduction was maintained with incremental doses of Pc. The ulnar nerve was stimulated with 0.1 Hz supramaximal stimuli of 0.1 ms duration via subcutaneous electrodes. In addition to the adduction force, the corresponding electromyogram (e.m.g.) of adductor pollicis was recorded. Hypo-, normo-, or hypercarbia was induced by mechanical IPPV adjusted to produce end-tidal carbon dioxide concentration of about 3.5%, 5.5% or 7.5%, respectively. Mean Pa_{CO_2} in the three groups at the end of the procedure were 24.8, 37.2 and 53.6 mm Hg, respectively. Towards the end of the operation neostigmine 0.035 mg kg^{-1} and atropine 0.0175 mg kg^{-1} were given at 90% block.

The recovery of twitch tension after neostigmine was slower in hypercarbic than in normo- and hypocarbic patients (14 min as against 8 min to 90%). The recovery times from 75% to 25% block correlated with Pa_{CO_2} ($r = 0.55$, $P<0.05$) and to pH_a values ($r = 0.47$, $P<0.05$). While 100% twitch was reached in hypo- and normocarbic patients, about 10% residual block was seen in hypercarbic patients. Fade in train-of-four (2 Hz) at recovery to plateau, however, was similar in all three groups. The recovery of e.m.g. amplitudes was not different in the three groups.

The results suggest that the opposing effect of hypercarbia on neostigmine antagonism of Pc-induced twitch suppression is a result of decreased contractility of the muscle fibres rather than a failure of neuromuscular transmission. The clinical significance of the measured depression of contractility induced by slight to moderate hypercarbia for the restitution of adequate muscle tone after anaesthesia is questionable.

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THE USE OF DI-ISOPROPYL PHENOL (ICI 35 868) AS THE MAIN ANAESTHETIC AGENT FOR BODY SURFACE OPERATIONS

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Di-isopropyl phenol is an i.v. anaesthetic which has been undergoing clinical trials for some years (Kay and Rolly, 1977). The drug is sparingly soluble in water and is administered in a solution containing Cremophor EL, though it is hoped that at a later date a new formulation may be devised.

The present studies were designed to determine the optimum induction dose and to assess recovery after intermittent administration. Di-isopropyl phenol was given over a period of 20 s in a dose of 0.5, 1.0, 1.5, 1.75 and 2.0 mg kg^{-1} to groups of patients undergoing minor gynaecological operations. Anaesthesia was then maintained with 70% nitrous oxide in oxygen and further doses of the i.v. agent as required. Only the last two doses consistently produced sleep in all patients.

Pain was experienced by some patients, but mainly when the drug was given into small veins in the back of the hand. Onset of anaesthesia was rapid and excitatory effects were rare. The reduction in arterial pressure and degree of respiratory depression were comparable to that seen after barbiturate anaesthesia. Recovery was rapid and appeared to compare with propanidid except that vomiting after operation was rare. Thirty patients were studied for 14 days with special reference to venous sequelae, which occurred in one.

In further series of 12 adults of both sexes undergoing body surface operations di-isopropyl phenol 2 mg kg^{-1} was given with further increments of 20 mg for operations lasting at least 45 min. Nitrous oxide in oxygen was again used to assist maintenance of anaesthesia. The technique is not as satisfactory as giving the drug by infusion but it enables assessment of the minimum dose requirement. There was little reduction in requirement over the period and again recovery was rapid when the nitrous oxide was discontinued.

Di-isopropyl phenol would appear to have a role both as an induction agent, where rapid recovery is desired, and for infusion techniques.

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EVALUATION OF RECOVERY—THE CONCEPT OF SYMPTOMATIC PSYCHOSIS ADAPTED FOR ANAESTHESIOLOGICAL CONSIDERATIONS

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TABLE I. *Recovery after different types of anaesthetics (mean ± SD)* *$P < 0.05$. *NLA = neuroleptanaesthesia; TST = transit syndrome test; 0–4 = full mental acuity*

	NLA	NLA + naloxone	Enflurane
n	20	10	20
Duration of anaesthesia (min)	182.0 ± 56	172.0 ± 61	179.0 ± 48
Time of awakening (min)	1.2 ± 3.3	1.1 ± 4.5	7.3 ± 6.3*
Time of extubation (min)	65.1 ± 44.4*	5.5 ± 3.5	6.9 ± 6.8
TST score			
Before operation	2.2 ± 1.9	1.8 ± 1.4	2.4 ± 2.9
30 min after operation	16.8 ± 6.4	12.9 ± 3.8*	16.9 ± 3.8
1 h after operation	11.4 ± 5.2	9.9 ± 3.0	10.8 ± 4.0
2 h after operation	10.0 ± 4.0	9.4 ± 3.0	8.6 ± 2.7
3 h after operation	8.1 ± 3.8	8.9 ± 3.0	7.1 ± 2.8

Symptomatic or function psychosis are non-specific reductions of efficiency which may occur in the course of pathological brain processes. They constitute a homogeneous, dynamic system of syndromes ranging from mild transit syndrome to unconsciousness and coma. Quantification is possible by means of psychopathometric tests developed by Wieck and co-workers, the function psychosis scale B test (FPSB) and the transit syndrome test (TST) (Wieck, 1978). While the FPSB covers the whole range of function psychosis, the TST begins with moderate consciousness clouding, but is able to differentiate more exactly. The aim of the present study was the quantitative evaluation of recovery using these bedside tests

Fifty patients were examined who had undergone tympanoplasty. Twenty patients received enflurane and 30 received neuroleptanaesthesia, of whom 10 were antagonized with naloxone. The anaesthesia was ended in strict accordance with clinical rules.

All three groups showed no differences as to age, sex, body weight, IQ-values and duration of anaesthesia. The neurolept-anaesthesia groups did not differ statistically in their drug requirement (e.g. diazepam 13.8 and 16.5 mg, fentanyl 1.01 and 0.94 mg, respectively). However, they needed twice as much alcuronium as the enflurane group (14.6 and 7.4 mg respectively), which may effect the differing dynamics of neuroleptic and inhalation anaesthesia.

Recovery data are shown in table I. Psychopathometric evaluation yielded an obvious decline in the TST scores after operation, which clearly remained less than the pre-operative values even after 3 h. All the patients revealed a severe transit syndrome after 30 min, a moderate syndrome after 1 and 2 h and mild after 3 h. The only exceptions were patients receiving naloxone who initially showed a brief improvement, but who afterwards did not behave better. The least favourable results occurred when neuroleptanaesthesia was not antagonized; the first TST values could only be obtained in patients in whom the tracheal tube had been removed: the real TST scores for 30 min and for 1 h are probably considerably worse in these patients. Correlation analysis of the data in this group strongly supports the clinical experience that the time of awakening depends on when the supply of nitrous oxide is ended, whereas the time of extubation is essentially determined by the time of the last fentanyl dose administered.

REFERENCE

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E.E.G. INDICES FOR EVALUATION OF DEPTH OF ANAESTHESIA: THE MEDIAN OF FREQUENCY DISTRIBUTION

H. STOECKEL, H. SCHWILDEN, P. LAUVEN AND H SCHÜTTLER
Institut für Anästhesiologie der Universität Bonn

Vegetative parameters are of limited value in evaluating depth of anaesthesia. The e.e.g. reflects the action of anaesthetics on the c.n.s. and offers the possibility of assessing the main pharmacological effect. In 48 cases (40 patients, eight volunteers) the e.e.g. was recorded on magnetic tape during anaesthesia for further off-line analysis. Etomidate, enflurane–nitrous oxide, fentanyl–nitrous oxide or etomidate–fentanyl were administered continuously.

We calculated.

(1) the power spectrum between 0.5 Hz and 32 Hz;
(2) the mean amplitude, defined as the standard deviation of the e.e g. amplitude;
(3) the proportion of total activity in the frequency bands: 0.5–2 Hz, 2–5 Hz, 5–8 Hz, 8–13 Hz, 13–32 Hz;
(4) the alpha-delta-index and the beta-delta-index defined as the ratio of activity in the bands 13–32 Hz and 0.5–5 Hz,
(5) the median of the power spectrum regarded as a frequency distribution.

The main results were:

(1) Several indices suited an examination of the depth of anaesthesia.
(2) The low-frequency band 0.5 Hz–2 Hz should not be neglected in spectral analysis; it may account for 60% of total activity during deep anaesthesia.
(3) The mean amplitude and other related amplitude measures are less suited because of variation between subjects.
(4) The median of frequency distribution proved to be the most stable index with good sensitivity to alternating states of anaesthesia. In all cases anaesthesia of moderate depth was characterized by a median less than 5 Hz
(5) The median does not reflect too deep anaesthesia with sufficient reliability as indicated by the appearance of burst suppressions. However, on the one hand too deep anaesthesia may be avoided by using dose regimens based on pharmacokinetic data; on the other hand burst suppressions are simple easily recognized patterns.

The median of frequency distribution combined with pattern recognition methods may be well suited for computer aided control of anaesthesia.

POSTER DEMONSTRATIONS

INJECTABLE BENZODIAZEPINES IN ANAESTHESIA

J. W. DUNDEE AND J. A. S. GAMBLE
Department of Anaesthetics, The Queen's University of Belfast, Northern Ireland

In general the benzodiazepines are poorly soluble in water and most of them are taken by mouth as tranquillizers, sedatives or hypnotics. However, organic solvents and lipophilic agents have been used to prepare solutions with varying degrees of success. Chlordiazepoxide (Librium) is soluble in water, but forms an unstable solution and requires large volumes.

Diazepam is generally dissolved in organic solvents, but the solution is viscid, painful on i.m. and i.v. injection, and is frequently followed by venous thrombosis. Absorption from i.m sites is poor. An alternative preparation made up in cremophor caused a high frequency of anaphylactic reactions. The latest preparation in Intralipid causes severe pain on the day following i.m. injection. After i.m injection we did not find such high plasma concentrations as after the normal solution.

Metabolism to a long-acting active hypnotic (nordiazepam) is a major disadvantage of diazepam. This does not occur with either flunitrazepam or lorazepam, both of which are soluble in water. Although flunitrazepam has many advantages over diazepam, its commercial use is limited to continental Europe and Canada A delayed onset of action is the main disadvantage of lorazepam, but it is a useful drug to produce a prolonged period of light sedation

Hopes are high that the new water soluble compound midazolam will compete with thiopentone as an i.v. induction agent (Sarnquist et al., 1980), but our findings are disappointing in this respect. Like diazepam, there is a wide individual variation in response The suggested "induction" dose is 0.3 mg kg^{-1} but even after 0.5 mg kg^{-1} not every patient is asleep 5 min after i.v. injection. We found it to have a shorter half-life than diazepam and did not detect an appreciable "second peak" effect (Dundee et al., 1980). Venous thrombosis, although infrequent, does occur following its use, but i.m. injection is not painful. Midazolam is worth a detailed study as a "light hypnotic" either alone, or with analgesics. This use is more likely than as an induction agent.

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A DOSE–RESPONSE RELATIONSHIP, AND CUMULATION STUDIES OF DIPRIVAN (ICI 35 868)

B. KAY and H. ADAM
University of Manchester

In a double-blind investigation of 100 unpremedicated patients, a dose–response relationship for Diprivan was determined, and compared with methohexitone. The patients were divided randomly into five groups of 20; three groups received Diprivan 1, 2 and 3 mg kg^{-1} respectively, and two methohexitone 1 or 2 mg kg^{-1}. Injection was over 20 s and the ensuing duration of sleep measured. Samples were taken to determine the decay of Diprivan blood concentrations after injection, and a mean blood concentration at which waking occurs. Methohexitone and Diprivan were equipotent at approximately 1.5 mg kg^{-1}, with similar effects over the clinical range of 1–2 mg kg^{-1}. Diprivan disappeared very rapidly from the blood according to a two-compartment model, with a very rapid initial redistribution phase and a slower elimination phase.

Compared with methohexitone, Diprivan provided a much smoother induction of sleep, with fewer side-effects.

In another investigation, sleep was induced by Diprivan 1 mg kg^{-1} and maintained by a similar injection whenever waking occurred, blood concentrations being determined at waking times. After the initial "induction" phase little evidence of accumulation was found, a dose of approximately 1 μg kg^{-1} being necessary to maintain sleep.

STUDIES ON BLOOD CONCENTRATIONS AFTER SPINAL AND EXTRADURAL ADMINISTRATION OF MORPHINE FOR THE TREATMENT OF CHRONIC AND ACUTE PAIN

W. DICK, B. KOSSMAN AND A. DRIESSEN
Center for Anesthesiology, University of Ulm

In a group of patients, most of whom had chronic pain because of carcinoma, we studied the effects of either intrathecal or extradural administration of morphine on the duration of analgesia, the respiratory frequency, minute ventilation and blood-gases and the blood concentration and urinary excretion of morphine. The blood and urine were also examined in patients in whom morphine was administered for postoperative pain relief or for pain relief in labour.

Effective pain relief could be obtained in a high percentage of patients up to 24 and 72 h in patients with chronic pain or between 2 and 72 h after operation.

There were no cardiovascular side-effects, but minute ventilation decreased up to 2 h after morphine administration and arterial P_{CO_2} increased.

After spinal administration the blood concentrations of morphine were almost negligible; extradural administration produced concentrations comparable to those following i.v. administration of the same dose.

EFFECTS OF CONTROLLED HYPOTENSION UNDER NITROPRUSSIDE AND FLUOTHANE, ON THE RENIN–ALDOSTERONE SYSTEM

J. L. ARROYO, R P. REINER, M. CEBRIAN, F. CARRASCOSA AND A. BERBIELA
Departamento de Anestesia y Reanimacion, Clinica Universitaria, Facultad de Medicina, Universidad de Navarra

We studied 24 patients with no previous disease divided into two similar groups, undergoing orthopaedic surgery of the limbs with a standard anaesthetic technique (thiopentone, pancuronium and morphine in divided doses; artificial ventilation with oxygen in 50% nitrous oxide). In group I, 10 min after incision halothane (1–3%) was administered, until a systolic pressure of 75–85 mm Hg was obtained and this was maintained for 30 min. In group II a similar degree and duration of hypotension was produced with sodium nitroprusside. Plasma renin activity (PRA), aldosterone (PA), ACTH, cortisol, Na^+, K^+, creatinine and osmotic pressure, were determined in both groups under basal conditions, at 10 min after incision, every 10 min throughout the period of hypotension, 30 min after it ended and 6 h after operation. Urinary Na^+, K^+, creatinine and osmotic pressure were assessed also. There was a significant increase ($P<0.01$), of mean PRA in both groups, although more pronounced in group I (10.2 ± 3.1 v. 8.1 ± 2.2 ng ml^{-1} h^{-1} in groups I and II respectively).

A greater increase of the PA was observed in group I (238 ± 81 and 292 ± 96 pg ml^{-1} in groups I and II respectively). The values of ACTH and cortisol were slightly increased in group II. The persistence of high concentrations of PRA 30 min after the period of hypotension had ended suggests the activity of the macula densa in increasing the secretion of renin.

EXPERIMENTAL UNILATERAL LUNG FLOODING. A MORPHOLOGICAL AND ULTRASTRUCTURAL STUDY

V. Chulia Campos, A. Llombart-Bosch, A, Peydro-Olaya, M. Lledó and F. J. Belda
Hospital Clínico Universitario de Valencia, Spain

In two groups of seven dogs (average weight 20 kg), the lungs were filled with 2 ml kg^{-1} of fluid (1/5 of tidal volume), after general anaesthesia with hexobarbitone 30 mg kg^{-1} and tracheobronchial intubation with a Carlens modified tube. The fluids used were Mediterranean sea water and swimming-pool water. The technique for introduction of the fluid was identical in the two series: right main bronchus was intubated and the fluid instilled. Thirty minutes later, the tube was removed. With this model the local effects of the liquid could be distinguished from those of acute hypoxia.

Twenty-four hours later, and without treatment, the dogs were sacrificed and biopsies of right and left lung performed. A clear difference was found between the swimming-pool water (vascular congestion, rupture of vessels, ruptured septa and haemorrhage) and the sea water (vascular congestion and acute inflammation, thickening and massive emigration of leucocytes and macrophages, and occasional alveolar oedema and haemorrhage).

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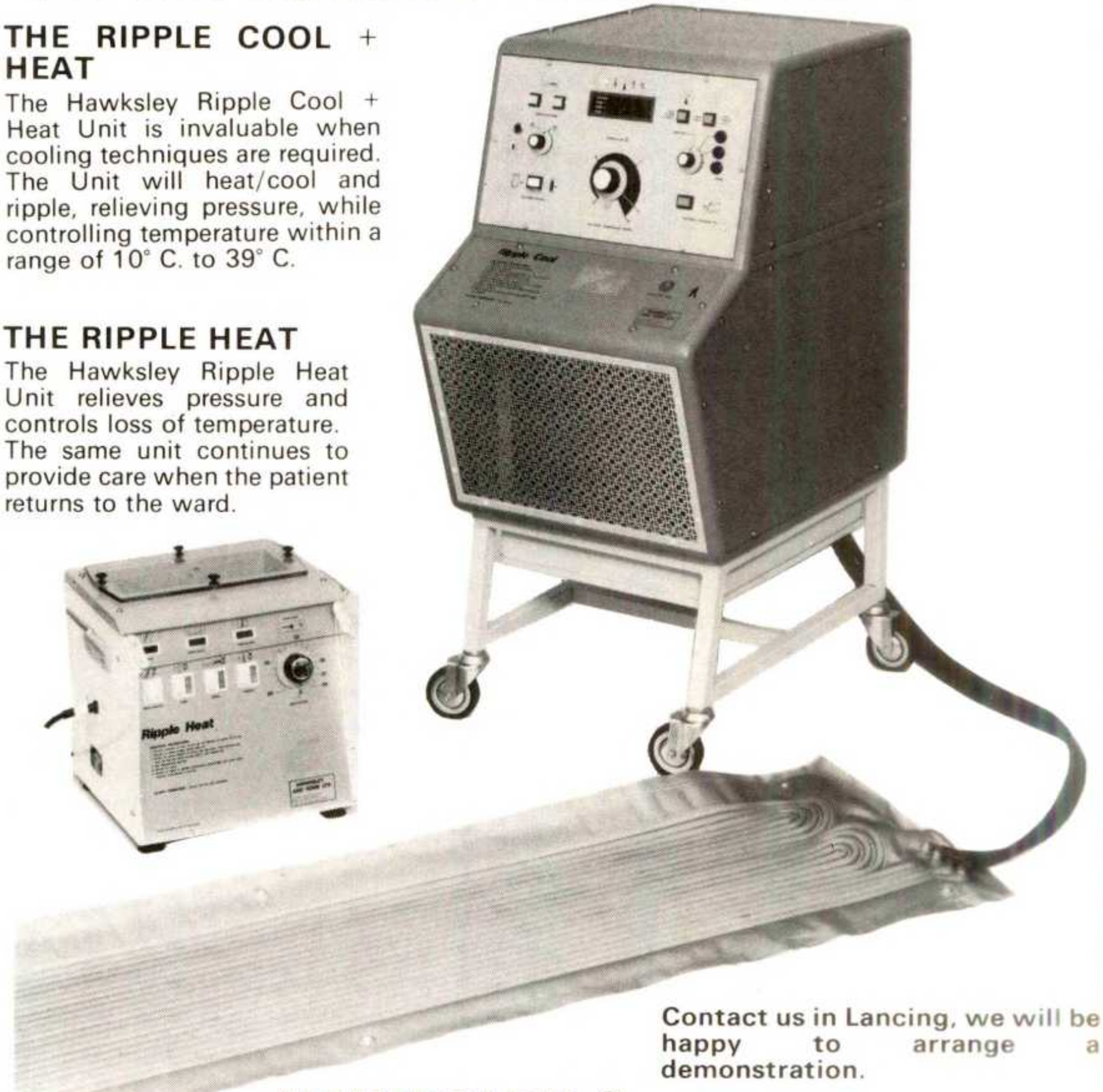

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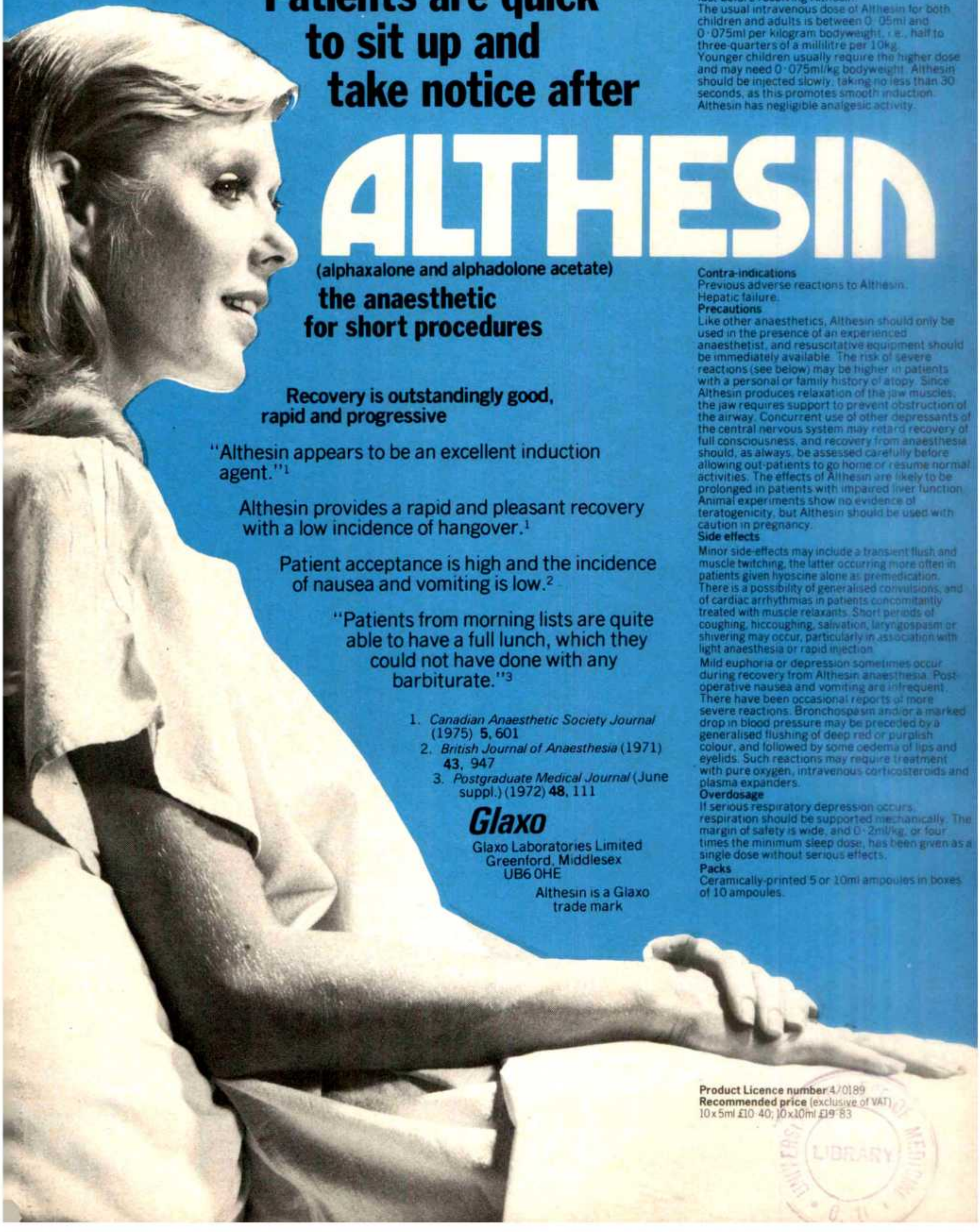

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1. *Canadian Anaesthetic Society Journal* (1975) **5**, 601
2. *British Journal of Anaesthesia* (1971) **43**, 947
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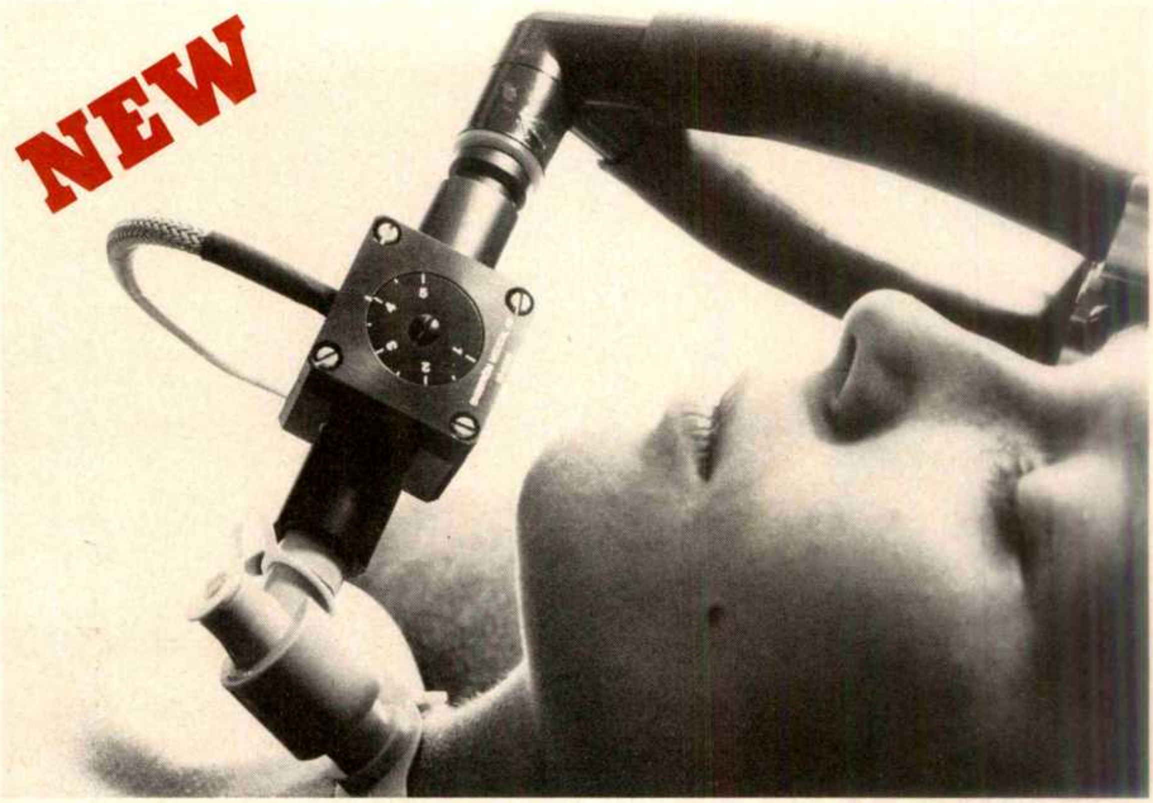

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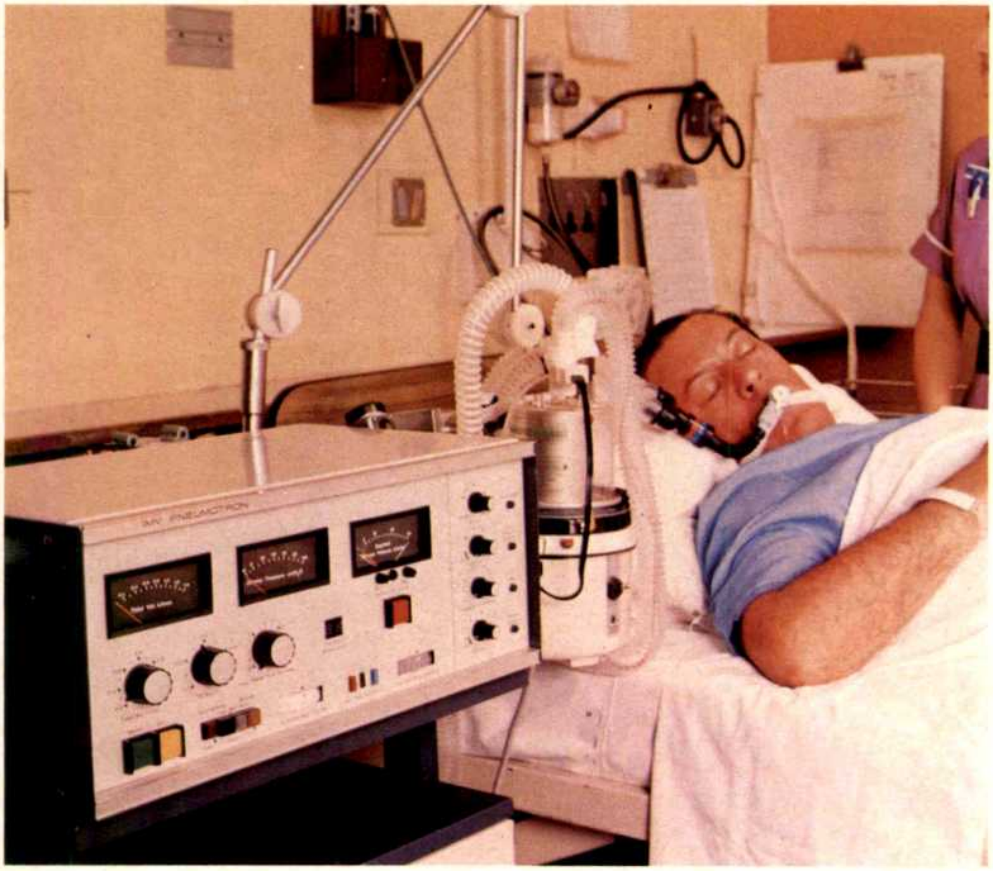

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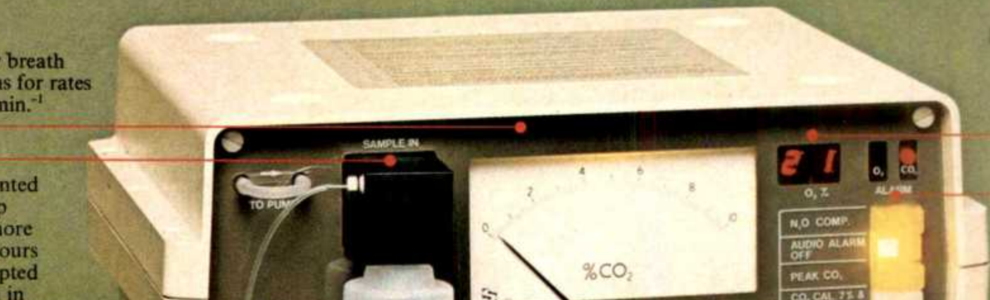

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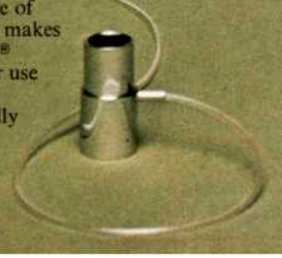

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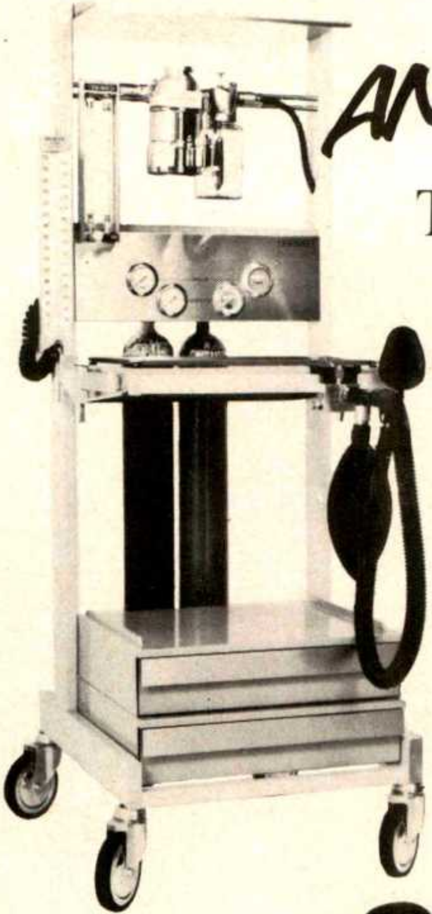

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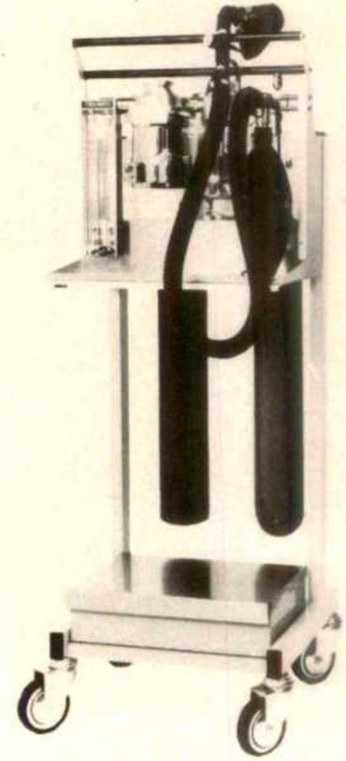

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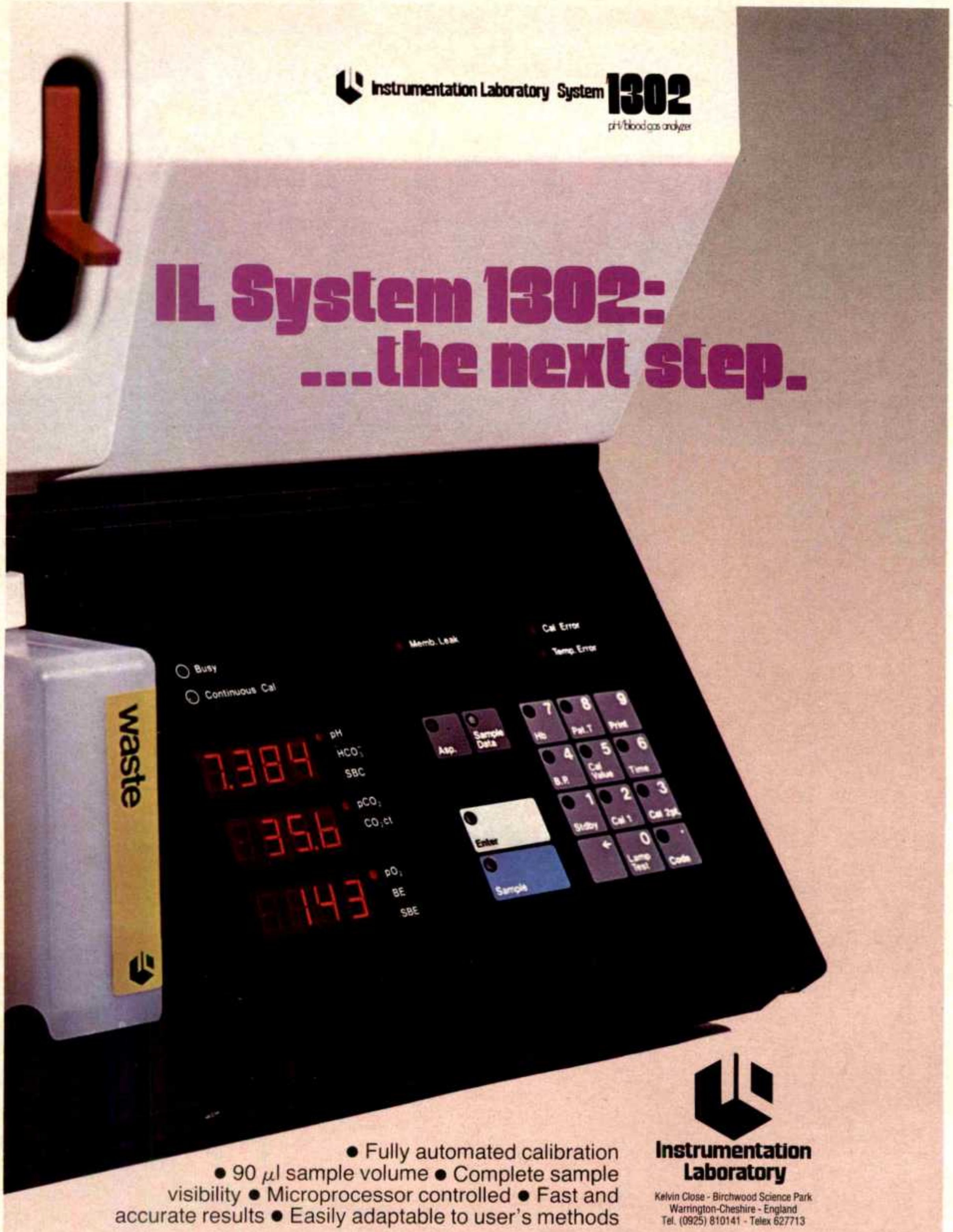

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BRITISH JOURNAL OF ANAESTHESIA

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EDITORIAL

METABOLISM AND ANAESTHESIA

Anaesthetists need to be able to assess and look after many aspects of the functions of their patients. Obviously, initially, the provision of good anaesthesia is essential with the selection of techniques appropriate for the patient, the operation and the surgeon. In association with this, maintenance of the oxygenation of the arterial blood and of a sufficient cardiac output should ensure that tissue hypoxia does not occur. In the past 20 years considerable work has led to a better understanding of the applied respiratory and circulatory physiology and pharmacology of anaesthesia. What is becoming obvious is that many of our techniques and drugs act not only directly on organs such as the heart, but also on the neural and endocrine systems that control the heart. Further, it is apparent that there are a number of controlling mechanisms.

Delivery of an adequate supply of oxygenated blood is not sufficient in itself to maintain function. In the short term it may be the most important activity and anaesthetists know the consequences of 3 or 4 minutes of cardiac arrest only too well. In the longer term it is equally important to look at what the tissues do with the oxygen. Put simply, the oxygen is used to burn substrates such as carbohydrates, fats and proteins to provide the energy necessary to maintain body temperature and to maintain intracellular ATP concentrations so that the cellular, tissue and organ function may be maintained.

This supply of substrate for energy production is as necessary as that of oxygen. Some cells have reserves of possible substrates—some such as adipocytes act as stores for the body. Some need a more continuous supply. The resources available to the body are summarized in table I of Stanley's first paper in this issue; the average man has some 125 000 kcal of reserve available and a normal daily intake of the order of 2% of that reserve. The majority is in the form of triglycerides in fatty tissue (80%) and most of the rest is in the proteins in muscle. Less than 1% is in the form of carbohydrates as either glycogen or glucose. Obviously, such a structurally diverse set of stores must be controlled in ways which ensure that those cells requiring substrates receive them in appropriate amounts. Control is also necessary, for most of us take in our energy sources intermittently, rather than continuously, and also in forms not always matching the tissue needs. Further, with a reasonably large store it is possible to cope with starvation and the generalized metabolic response to trauma.

The biochemical pathways involved in transforming carbohydrates, fats and proteins into ATP are now well established. Those wishing for a clear, precise, illustrated account of these to refresh their memories will find Stryer's textbook an excellent source (Stryer,1981). In this issue the first four papers are devoted to summarizing the state of knowledge as to how these metabolic pathways are controlled and integrated to match supply with demand in the normal subject and in starvation. Further details of the biochemical mechanisms of regulation will be found in Newsholme and Start (1973).

The effects of anaesthesia and surgery on metabolism and metabolic regulation are complex. With knowledge and with increasing skill it is possible to modify or abolish some of the normal reactions to injury. Traynor and Hall end their review by posing an important question: how can we modify these responses and are they necessary? To be injured and without aids such as blood volume replacement, attention to lung function, the prevention of pain and the provision of nutrition (with insulin if need be) is a different proposition than being in an environment where these facilities are available.

The final two papers deal with more practical matters. In the first, Goode looks at the problem of who needs nutritional support and how the need should be assessed. Quantitation is now possible. In the second, Powell-Tuck describes the principles underlying current practice and shows how refinements in technique are adding to the usefulness and safety of the methods available.

Finally, it is a pleasure to acknowledge the considerable help given by Professor Newsholme of the Department of Biochemistry in Oxford in the production of this issue.

J. Norman

REFERENCES

Newsholme, E. A., and Start, C. (1973). *Regulation in Metabolism*. London: J. Wiley.

Stryer, L. (1981). *Biochemistry*, 2nd edn. San Francisco: W. H. Freeman.

Br. J. Anaesth. (1981) 53, 123

THE GLUCOSE–FATTY ACID CYCLE

Relationship between glucose utilization in muscle, fatty acid oxidation in muscle and lipolysis in adipose tissue

J. C. STANLEY

This series of articles is concerned with how carbohydrate, lipid and amino acid metabolism in different tissues is integrated for the benefit of the whole animal. The tissues of the body oxidize a variety of organic compounds for production of biological energy in the form of ATP. These compounds include glucose, fatty acids, ketone bodies and some amino acids and for the purpose of these articles they can be grouped together under the term metabolic fuels. They are obtained either from the diet or from storage molecules such as glycogen, triacylglycerol and protein. It is crucial for the wellbeing of the animal that at least one of these metabolic fuels is always available in the bloodstream or the tissue despite large fluctuations in the rate of fuel utilization by the tissues or in the rate of fuel production from endogenous or exogenous sources. There is a vital need for the rate of production of a fuel to be regulated precisely in relation to its rate of utilization and for the rate of production and utilization of all fuels to be satisfactorily integrated. The present series of articles presents the author's own view of how this might be achieved.

TABLE I. *Fuel reserves in a 70-kg human subject*

Fuel	Tissue	Fuel reserve (average man) kcal	Fuel reserve (average man) g
Triglyceride	Adipose tissue	100 000	15 000
Glycogen	Liver	200	70
	Muscle	400	120
Glucose	Body fluids	40	20
Protein	Muscle	25 000	6000

This table has been taken from *Regulation in Metabolism* by Eric A. Newsholme and Carole Start, with kind permission of the publishers (John Wiley and Sons Ltd).

The metabolism of higher animals suffers from several disadvantages which become apparent in conditions of carbohydrate deprivation such as starvation. First, certain tissues such as red blood cells are completely dependent, and others such as brain and central nervous system are partially dependent, upon glucose as a metabolic fuel. Therefore, the supply of glucose to such tissues must be maintained. Second, the capacity of the liver to store glucose as glycogen is limited, in marked contrast to the capacity of the adipose tissue to store triacylglycerol (table I). Liver glycogen, therefore, cannot maintain the glucose supply for prolonged periods and must be augmented by the synthesis of glucose, that is gluconeogenesis from other endogenous sources, in particular the amino acid alanine derived from the degradation of muscle protein. Third, higher animals are unable to synthesize glucose from fatty acids and as a result are unable to make use of the major portion of stored triacylglycerol for this purpose. Nevertheless, adipose tissue triacylglycerol can contribute to the supply of glucose directly by providing glycerol, a gluconeogenic precursor, and indirectly by providing fatty acids and, ultimately, ketone bodies which are oxided in preference to glucose by some tissues. It is apparent from these considerations that complex control mechanisms are necessary for integrating the production and utilization of the various metabolites mentioned above.

Broadly speaking, the control mechanisms responsible for the conservation of glucose in conditions of carbohydrate deprivation involve inhibition of the pathways of glucose utilization and activation of the pathways of glucose production. These metabolic adaptions are integrated so that the blood glucose concentration is maintained relatively constant during

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J. C. STANLEY, PH.D., Department of Biochemistry, Manchester University, Oxford Road, Manchester M13 9PL.

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starvation, in marked contrast to the fatty acid or ketone body concentrations (table II). In this series of articles the regulation of glucose utilization through the availability of fatty acids will be discussed first and the role of muscle as the site of fatty acid utilization and adipose tissue as the site of fatty acid production will be described. Then the regulation of glucose utilization through the availability of ketone bodies will be discussed and the role of the liver in their synthesis and of brain, kidney cortex and small intestine in their utilization will be described. The regulation of glucose production will include a discussion of the role of liver glycogen and the regulation of gluconeogenesis will be discussed in relation to the tissues which supply gluconeogenic precursors, namely skeletal muscle, adipose tissue and red blood cells and the tissues which synthesize glucose, namely liver and kidney cortex. Finally, some ideas concerning the mechanism of action of hormones on metabolism will be described.

TABLE II. *Concentrations of glucose, long chain fatty acids and ketone bodies during starvation in man*

	Serum (or plasma) concentrations (mmol litre^{-1})							
		Days of starvation						
Fuel	Fed	1	2	3	4	5	6	8
Glucose	5.5	4.7	4.1	3.8	3.6	3.6	3.5	3.5
Long chain fatty acids	0.30	0.42	0.82	1.04	1.15	1.27	1.18	1.88
Ketone bodies	<0.01	0.03	0.55	2.15	2.89	3.64	3.98	5.34

This table has been taken from *Clinics in Endocrinology and Metabolism,* Volume 5 Number 3, with kind permission of the publishers (W. B. Saunders Company Ltd).

The inhibition of glucose utilization in muscle by the oxidation of fatty acids

Experiments with isolated *in vitro* muscle preparations have shown that the oxidation of fatty acids inhibits the rate of carbohydrate utilization. Thus perfusion of the isolated rat heart with fatty acids in the presence of glucose inhibits the rate of glucose uptake and glycolysis (Garland, Newsholme and Randle, 1964). This inhibition of glucose utilization is dependent upon the oxidation of the fatty acids rather than their presence, since the inhibitory effect is abolished by respiratory poisons. Similar results were obtained using the isolated rat diaphragm. Furthermore, perfusion of the rat hindquarter with fatty acids in the presence of glucose inhibits the rate of glucose uptake and glycogen depletion in red skeletal muscle providing the preparation is well oxygenated (Rennie and Holloszy, 1977). It can be concluded, therefore, that in heart, diaphragm and red skeletal muscle fatty acids are oxidized in preference to glucose and that fatty acid oxidation specifically inhibits the rate of carbohydrate utilization by these muscles.

These conclusions are confirmed by studies of muscle metabolism *in vivo.* Under conditions such as starvation and prolonged exercise, in which the blood fatty acid concentration increases, it can be shown that the respiratory quotient decreases, indicating a shift from carbohydrate to lipid utilization. It is important to appreciate that this shift occurs in the absence of any appreciable decrease in the blood glucose concentration and hence that lipid-derived fuels are being oxidized in preference to glucose. Using arterial and coronary sinus catheterization techniques, a negative correlation between the plasma fatty acid concentration and the rate of glucose utilization by the human heart *in vivo* was demonstrated. A similar relationship has been shown between the rate of pyruvate oxidation by skeletal muscle during excercise and the plasma fatty acid concentration. Hence the oxidation of fatty acids by muscle *in vivo* inhibits glucose utilization or oxidation, or both.

The biochemical mechanism whereby the oxidation of fatty acids by muscle inhibits glucose utilization has been studied using two experimental approaches. The kinetic properties of purified key enzymes of carbohydrate utilization have been studied *in vitro* in order to identify possible regulator molecules. Then the concentration changes in these candidate regulator molecules are measured in the muscle *in vivo.* This approach identifies which of the regulators is of importance in mediating the inhibition of glucose utilization by fatty acid oxidation. The above approaches have led to the elucidation of the following sequence of events.

The oxidation of fatty acids in muscle occurs within the mitochondria and leads to an increase in the concentration ratio acetyl-CoA : CoA within this compartment. An increase in this concentration ratio inhibits the mitochondrial multienzyme complex pyruvate dehydrogenase, which converts pyruvate into acetyl-CoA. This reaction represents a loss of carbohydrate to the body since, once pyruvate has been metabolized by this enzyme to acetyl-CoA, it is committed to oxidation. Furthermore, since pyruvate that is not oxidized is released from the tissue either as lactate or alanine, which are both excellent gluconeogenic precursors, the oxidation of fatty acids in muscle conserves glucose, by inhibiting pyruvate dehydrogenase activity.

A second consequence of the increase in the mitochondrial acetyl-CoA concentration is an increase in the mitochondrial citrate concentration through the reaction catalysed by citrate synthase. Citrate can cross the inner mitochondrial membrane via a specific transport system and hence the concentration of cytoplasmic citrate also increases when fatty acids are oxidized by muscle. Citrate potentiates the inhibition, by ATP, of phosphofructokinase, a key glycolytic enzyme which catalyses the conversion of fructose-6-phosphate to fructose-1,6-diphosphate.

The inhibition of phosphofructokinase by citrate in turn leads to an accumulation of its substrate fructose-6-phosphate within the cytoplasm. Fructose-6-phosphate and glucose-6-phosphate are maintained close to equilibrium in a reaction catalysed by phosphoglucoisomerase. Consequently, an increase in the concentration of fructose-6-phosphate will be accompanied by an increase in the concentration of glucose-6-phosphate. Glucose-6-phosphate is an inhibitor of hexokinase and phosphorylase so that, when muscles oxidize fatty acids, the phosphorylation of glucose, derived either from the bloodstream or endogenous glycogen, will be inhibited.

This concerted mechanism for the inhibition of glucose utilization in muscle by the oxidation of fatty acids is illustrated in figure 1.

The transport of glucose across the cell membrane may also be inhibited when fatty acids are oxidized by muscle, so that this provides a further control point for glucose utilization in this tissue. However, the mechanism of this effect is at present unknown.

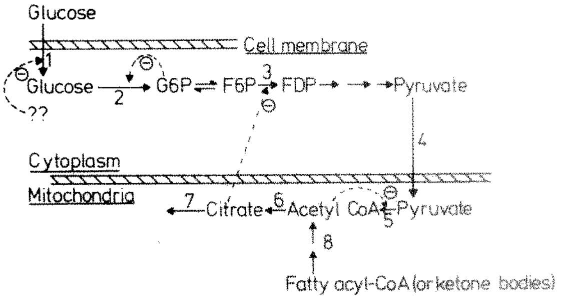

FIG. 1. Inhibition of glucose utilization in muscle by fatty acid oxidation. 1 = Glucose transport across cell membrane; 2 = hexokinase; 3 = phosphofructokinase; 4 = pyruvate transport across inner mitochondrial membrane; 5 = pyruvate dehydrogenase; 6 = citrate synthase; 7 = tricarboxylic acid cycle; 8 = β-oxidation of fatty acids.

The discussion so far has demonstrated that the provision of fatty acids to heart, diaphragm and red skeletal muscle results in their oxidation by muscle and the consequent inhibition of glucose utilization. This mechanism contributes towards the conservation of glucose in situations such as starvation where the concentration of fatty acids in the blood is high. Since the rate of fatty acid oxidation by these muscles is dependent upon the fatty acid concentration in the blood, the rate of fatty acid oxidation by muscle is controlled by the rate of mobilization of fatty acids into the bloodstream. The source of these fatty acids is adipose tissue and, therefore, factors which regulate the rate of release of fatty acids from this tissue will in turn regulate the rate of their oxidation by muscle. This subject is discussed in the next section.

For a fuller discussion of the inhibition of glucose utilization in muscle by the oxidation of fatty acids the reader is referred to Newsholme and Start (1973).

Regulation of fatty acid mobilization from adipose tissue

Adipose tissue triacylglycerol is the major fuel reserve in man. This fuel reserve is made available to the tissues of the body as non-esterified fatty acids which are released into the blood by adipose tissue following the intracellular hydrolysis of triacylglycerol, a process referred to as lipolysis. Since fatty acids are relatively insoluble in water, they are transported in the blood bound to the protein albumin. The rate of release or mobilization of fatty acids from adipose tissue increases under certain conditions including starvation, sustained exercise and physical or psychological stress. Increased fatty acid mobilization results in two major metabolic adaptations, namely an increased rate of fatty acid oxidation in muscle and an increased rate of ketone body synthesis in the liver. It is, therefore, of crucial importance that the rate of fatty acid mobilization should be controlled in relation to the rates of fatty acid utilization by these tissues. The rate of fatty acid mobilization is regulated by a number of factors including sympathetic nervous activity, the concentration of circulating hormones (e.g. insulin) and the concentration of certain metabolites in the blood (e.g. ketone bodies, lactate). These factors are further discussed below.

The mobilization of fatty acids involves hydrolysis of triacylglycerol followed by the transport of the fatty acids across the membrane of the adipocyte. Transport occurs by simple diffusion and is, therefore, proportional to the fatty acid concentration gradient. However, the intracellular fatty acid concentration is not determined by the rate of lipolysis only, since a proportion of the fatty acid may be esterified. Hence factors which regulate the rate of re-esterification will also regulate the rate of fatty acid mobilization. Since such factors are not well understood at the present time, the following discussion will be confined to factors which regulate the rate of lipolysis and their consequent effect upon fatty acid mobilization. Nevertheless, the simultaneous activity of both the lipolytic pathway and the re-esterification pathway has an important role to play in increasing the sensitivity of control over fatty acid mobilization. This subject is also discussed below.

Adipose tissue triacylglycerol is hydrolysed to a mixture of fatty acids and glycerol in a three-step process, each step catalysed by a separate enzyme. Of the three enzymes concerned, triglyceride lipase is the most important since it catalyses a flux-generating step (Newsholme and Crabtree, 1979). The role of such an enzyme in a metabolic pathway is to generate a flux to which all the other enzyme-catalysed reactions in the pathway respond. Triglyceride lipase generates the flux through both lipolysis in adipose tissue and fatty acid oxidation in muscle, since a change in the rate of supply of fatty acids to muscle inevitably leads to a change in the rate of their oxidation. Hence in this case the pathway concerned spans two tissues. An enzyme which catalyses a flux-generating step has several characteristics. First, it catalyses a non-equilibrium reaction *in vivo* and second, it approaches saturation with its substrate *in vivo*. As a result the activity of the enzyme which catalyses the flux-generating step is independent of changes in the concentration of pathway-substrate and responds only to factors which are external to the pathway. Hence a flux-generating step can generate a steady-state flux to which all other reactions in the pathway adapt. It is, therefore, an extremely important control site. The activity of triglyceride lipase is regulated by a number of hormones, all of which act by mechanisms which involve changes in the concentration of regulators which are external to the pathway. One major difficulty in this field is the remarkable species variation in the response of lipolysis to hormones.

The hormonal regulation of adipose tissue lipolysis has been studied *in vitro* by measuring the rate of glycerol release from isolated adipose tissue preparations of the rat, for example epididymal fat pads or adipocytes and caution must be used in extrapolation of these findings to other animals. The results of such studies enable hormones to be classified as lipolytic or antilipolytic. Lipolytic hormones for the rat include catecholamines, glucagon, growth hormone in the presence of glucocorticoids, ACTH and possibly other pituitary hormones. Lipolytic hormones for man clude the catecholamines and TSH. Insulin and prostaglandins E_1 and E_2 are antilipolytic agents in both the rat and man. Some of these hormones may be involved in the stimulation of lipolysis *in vivo* during conditions of stress, prolonged exercise and starvation.

The rate of fatty acid mobilization increases in response to stress and prolonged exercise. It is likely that these effects are mediated through increased sympathetic activity, resulting in the release of noradrenaline, a lipolytic agent, from nerve endings in the tissue. The mechanism of action of noradrenaline on triglyceride lipase activity and hence lipolysis is comparatively well understood. The initial event is the binding of noradrenaline to a receptor on the surface of the adipocyte cell membrane. This event is responsible for the activation of the membrane-bound enzyme adenyl cyclase which synthesizes cAMP from ATP in the cytoplasm. An increase in the concentration of cAMP activates cAMP-dependent protein kinase, one of the substrates of which is triglyceride lipase. The cAMP-dependent protein kinase phosphorylates triglyceride lipase at the expense of ATP and activates the enzyme since the phosphorylated form is more active than the dephosphorylated form. As a result the mobilization of fatty acids from adipose tissue increases providing tissues such as muscle with an alternative fuel to glucose. During conditions of stress and prolonged exercise, the availability of an alternative fuel allows the conservation of glucose and prevents the hypoglycaemia that could result from a massive increased demand for metabolic fuels under these conditions. During starvation, the rate of fatty acid mobilization and the plasma fatty acid concentration increase. Changes in the concentration of several circulating hormones may mediate this effect, but since lipolytic hormones are species-specific, the following discussion refers to the rat but not to man. During starvation the concentration of insulin, an antilipolytic hormone, decreases. As a consequence, lipolysis will be de-inhibited. The mechanism of the inhibitory action of insulin on lipolysis is not well understood. However, insulin can decrease cAMP concentrations previously increased by lipolytic hormones, hence inhibiting cAMP-dependent protein kinase and triglyceride lipase activity. This mechanism may explain, at least in part, the antilipolytic activity of insulin. The concentration of circulating growth hormone and glucagon increases during starvation. Since both these hormones are lipolytic in the rat an increase in their concentrations may contribute towards the stimulation of lipolysis during starvation. Glucagon stimulates lipolysis by the same mechanism as catecholamines. Growth hormone, the lipolytic activity of which is seen only in the presence of glucocorticoids and takes longer to develop, acts by a different mechanism. It is thought that growth hormone stimulates the synthesis of adenyl cyclase and hence, as starvation proceeds growth hormone progressively increases the capacity of other lipolytic hormones to increase the cAMP concentration.

Changes in the concentration of circulating hormones during stress, sustained exercise and starvation may partly explain the increase in the rate of lipolysis under these conditions. However, an additional feedback control is provided by changes in the ketone body concentration. This control mechanism is discussed in more detail later on.

Isotopic techniques have shown that, in adipose tissue, the pathways of lipolysis and esterification are simultaneously active. Hence a proportion of the fatty acids formed by the hydrolysis of triacylglycerol are esterified and hence triacylglycerol is resynthesized. This triglyceride–fatty acid cycle is illustrated in figure 2. One apparent disadvantage of this substrate cycle is that the activation of fatty acids before esterification with glycerol phosphate is an ATP-requiring reaction. Hence the operation of the triglyceride fatty acid substrate cycle consumes ATP and could be regarded as energetically wasteful. However, one advantage of this substrate cycle is that it increases the sensitivity of control over the mobilization of fatty acids from adipose tissue. Therefore, the disadvantage of ATP utilization in this cycle is balanced by the advantage of improved sensitivity of control over fatty acid mobilization. For a fuller discussion of the regulation of fatty acid mobilization adipose tissue the reader is referred to Hales, Luzio and Siddle (1978).

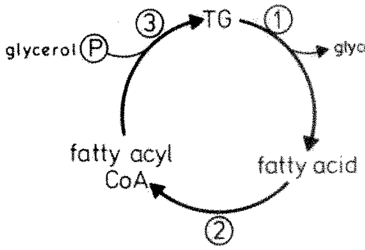

FIG 2. The triglyceride fatty acid cycle in adipose tissue. 1 = Lipolysis; 2 = activation of fatty acids; 3 = esterification of fatty acyl-CoA.

The glucose–fatty acid cycle

The concept of the glucose–fatty acid cycle seeks to explain the reciprocal relationship *in vivo* between, on the one hand the rate of glucose utilization in muscle and, on the other hand, the rate of fatty acid mobilization from adipose tissue and oxidation in muscle. These metabolic relationships serve to maintain the blood glucose concentration relatively constant despite large changes in the rates of production and utilization of glucose. The concept of the glucose–fatty acid cycle was proposed by Randle and others (1963). Originally the results of *in vitro* experiments using isolated muscle and adipose tissue preparations, some of which have been mentioned in the previous two sections, were used to formulate the theory of the glucose–fatty acid cycle which applies to the whole animal. However, evidence in support of the cycle has now been obtained from *in vivo* experiments. Since the concept of the glucose–fatty acid cycle was originally proposed, it has been found necessary to extend the cycle to include ketone bodies. However, in this section the original concept of the glucose–fatty acid cycle is discussed, with some evidence in support of the cycle. A discussion of the extended cycle and the physiological role of ketone bodies is provided in the next paper.

The glucose–fatty acid cycle is illustrated in figure 3. The theory of the cycle states that when the blood glucose concentration and particularly when the liver glycogen concentration decreases, then fatty acids are mobilized from adipose tissue. As a result the blood fatty acid concentration increases and fatty acids are oxidized by muscle. The oxidation of fatty acids by muscle specifically inhibits glucose utilization in this tissue. In the original concept of the cycle an increase in the blood glucose concentration was considered to be the major factor reducing fatty acid mobilization and decreasing the blood fatty acid concentration. However, it is considered currently that the major factor responsible for reducing the mobilization of fatty acids after, for example, refeeding a starved subject, is the increase in the concentration of insulin. This causes a decrease in the rate of fatty acid oxidation in muscle so that the rate of glucose utilization increases and consequently the blood glucose concentration will be maintained close to normal (fig. 3). This control mechanism allows rates of fatty acid oxidation, glucose utilization and fatty acid mobilization to be controlled by changes in the blood glucose concentration. Hence the glucose–fatty acid cycle allows the blood glucose concentration to be maintained relatively constant at the expense of the fatty acid concentration in the blood.

Some evidence for the operation of the glucose–fatty acid cycle *in vivo* has been obtained. First, the above theory predicts that an increase in the blood fatty acid concentration should decrease the rate of glucose utilization and hence impair glucose tolerance. The blood fatty acid concentration in human subjects *in vivo* can be increased either by a triglyceride meal followed by a heparin injection or by injecting noradrenaline, a lipolytic hormone. Increase of the blood fatty acid concentration by these experimental procedures decreases the rate of peripheral glucose utilization and impairs glucose tolerance. Second, the above theory predicts that, when the fatty acid concentration decreases, the rate of glucose utilization should increase and hence glucose tolerance should improve. The administration of nicotinic acid, an antilipolytic agent, to human subjects decreases the fatty acid concentration in the blood and improves glucose tolerance. Third, the above theory predicts that, if fatty acid oxidation is inhibited, the rate of glucose utilization should increase and consequently the blood glucose concentration should decrease. It has been shown that inhibitors of fatty acid oxidation such as pent-4-enoic acid when administered to human subjects are hypoglycaemic (Newsholme and Start, 1973).

The glucose–fatty acid cycle plays a role in a number of physiological conditions. Starvation increases the fatty acid concentration in the blood

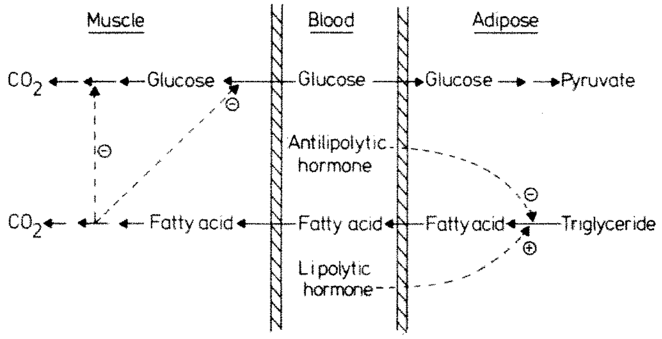

FIG. 3. The glucose–fatty acid cycle.

as a result of an increased rate of fatty acid mobilization from adipose tissue. The fatty acids are oxidized in muscle, so inhibiting glucose utilization in this tissue. As a result glucose will be conserved for those tissues which depend upon it as a metabolic fuel, for example red blood cells. Refeeding will result in an increase in the blood glucose concentration. Hence under these circumstances the inhibition of glucose utilization in muscle must be reversed in order to prevent an excessive increase in the blood glucose concentration. Absorption of glucose from the gut causes an increase in the glucose concentration in the hepatic portal vein which stimulates the secretion of insulin. It is generally accepted that the primary role of insulin in refeeding is stimulation of the membrane transport of glucose in adipose tissue and muscle. Hence the rate of glucose utilization by these tissues increases and prevents an excessive increase in the blood glucose concentration after refeeding. This may be termed the anabolic role of insulin. However, the author considers that the antilipolytic activity of insulin may be of greater importance in promoting glucose utilization after refeeding. Insulin inhibits fatty acid mobilization from adipose tissue, which decreases the rate of fatty acid oxidation in muscle and hence increases the rate of glucose utilization in this tissue. This role of insulin in the regulation of the blood glucose concentration may be called the homeostatic role of insulin (Newsholme, 1977). The glucose–fatty acid cycle also prevents hypoglycaemia during sustained exercise. Thus the mobilization of fatty acids during this type of exercise will inhibit glucose utilization in muscle and so conserve glucose.

The glucose–fatty acid cycle goes some way towards accounting for the relative constancy of the blood glucose concentration. However, extending the cycle to include the physiological role of ketone bodies as substrate and signal provides a more satisfactory explanation. The glucose–fatty acid ketone body cycle is discussed in the next paper (Stanley, 1981).

For further discussion of the glucose–fatty acid cycle, the reader is referred to Newsholme (1976).

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THE GLUCOSE–FATTY ACID–KETONE BODY CYCLE

Role of ketone bodies as respiratory substrates and metabolic signals

J. C. STANLEY

In this paper, the glucose–fatty acid cycle is extended to include the ketone bodies acetoacetate and 3-hydroxybutyrate. The physiological roles of acetoacetate and 3-hydroxybutyrate as respiratory substrates and of 3-hydroxybutyrate as a metabolic signal are discussed. The paper includes descriptions of the regulation of ketogenesis in the liver, the use of ketone bodies as alternative fuels to glucose in the brain, the kidney cortex and the small intestine and the regulation of insulin secretion by the β-cells of the endocrine pancreas and of lipolysis in adipose tissue by 3-hydroxybutyrate. Emphasis will be placed upon the ability of ketone bodies to integrate the metabolism of different tissues and the contribution ketone bodies make towards glucose conservation in conditions of carbohydrate deprivation such as starvation.

Acetoacetate and 3-hydroxybutyrate, with acetone, were first discovered in the urine of diabetic patients. This association with a pathological condition led to the idea that these organic compounds were by-products of metabolism. Although it is unlikely that acetone has any physiological role, both acetoacetate and 3-hydroxybutyrate are of crucial physiological importance as described below. In an attempt to get away from the idea that ketone bodies are by-products of metabolism, some authors refer to acetoacetate and 3-hydroxybutyrate as the ketoacids. However, in this series of articles the term ketone bodies will be used to describe acetoacetate and 3-hydroxybutyrate. Nevertheless, it is possible to distinguish between the physiological ketosis of prolonged starvation when the plasma ketone body concentration increases to approximately 8 mmol $litre^{-1}$ and the pathological ketosis of diabetes when the plasma ketone body concentration may reach 30 mmol $litre^{-1}$.

Diabetes is not the only pathological condition in which the ketone body concentration in the blood increases. Some hypoglycaemic conditions of childhood are characterized by a deficiency in hepatic glycogen synthase activity and hence the liver is unable to synthesize glycogen. After an overnight fast the ketone body concentration in the blood of such children increases to about 8.5 mmol $litre^{-1}$. Since ketone bodies inhibit the release of the gluconeogenic precursor alanine from muscle (see later), then the rate of gluconeogenesis in such children is also depressed. Hence the low blood glucose concentration (1.5 mmol $litre^{-1}$) seen after an overnight fast is a consequence of both an inadequate liver glycogen store and a low rate of gluconeogenesis (Aynsley-Green, Williamson and Gitzelmann, 1977).

As can be seen from table II in the previous paper (Stanley, 1981), the ketone body concentration in the blood can vary over a 20-fold range during starvation. Such changes in concentration are not found in the case of other blood metabolites such as glucose and fatty acids. This emphasizes the potential of ketone bodies as metabolic signals for integrating the metabolism of different tissues.

Inhibition of glucose utilization by the oxidation of ketone bodies in the brain, kidney cortex and small intestine

In the postabsorptive state the brain uses approximately 120 g of glucose per day. This glucose is completely oxidized to carbon dioxide and water via the pathways of glycolysis, the tricarboxylic acid cycle and the respiratory chain. Hence glucose utilization by the brain represents loss of carbohydrate to the body which must be replaced either from dietary sources or, during starvation, from endogenous sources such as liver glycogen or gluconeogenesis. Since liver glycogen can only provide sufficient glucose for the brain for about

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24 h during starvation, then either glucose must be provided by gluconeogenesis or the brain must oxidize some alternative fuel. Although gluconeogenesis does provide glucose for the brain during starvation this creates an additional problem since the amino acid alanine, the major precursor for gluconeogenesis in the liver, is derived from the degradation of muscle protein. Since muscle protein is essential for the survival of the animal it cannot be degraded indefinitely to satisfy the glucose requirement of the brain. Therefore, it is necessary for the brain to use an alternative fuel to glucose during starvation and hence allow the conservation of body protein.

Using arteriovenous catheterization techniques it has been shown that, in obese patients undergoing a 5–6-week period of therapeutic starvation, the glucose requirement of the brain decreases to about 35 g per day (Owen et al., 1967). Hence glucose utilization by the brain during prolonged starvation decreases by about 70%. This study also demonstrated that, as the concentration of ketone bodies in the blood increased during starvation, so did the rate of ketone body utilization. The capacity of the brain for ketone body oxidation was demonstrated by the finding that all the enzymes necessary for ketone body oxidation were present in this tissue. Thus the brain has the capacity for ketone body oxidation which is used in conditions such as starvation when the plasma ketone body concentration increases. It should, however, be pointed out that even in prolonged starvation ketone bodies do not completely replace glucose as a metabolic fuel. Hence gluconeogenesis must still provide about 35 g of glucose per day to the brain in prolonged starvation. It is unclear whether this represents an absolute requirement for this amount of glucose by the brain or whether, at high concentrations of ketone bodies, the brain could use less glucose.

The mechanism whereby ketone body oxidation inhibits glucose utilization in the brain is likely to be similar to the mechanism whereby fatty acid oxidation inhibits glucose utilization in muscle. The oxidation of ketone bodies, like the oxidation of fatty acids, will increase the concentration of acetyl-CoA within the mitochondria. It is likely that the resultant increase in the concentration ratio acetyl-CoA : CoA inhibits pyruvate dehydrogenase activity. Furthermore, it has been shown that, in the rat brain, the oxidation of ketone bodies increases the concentration of citrate and inhibits the activity of phosphofructokinase. This will presumably lead to a decrease in the activity of hexokinase via an increase in the concentration of the inhibitor glucose-6-phosphate. However, more work needs to be done in this area; in particular the effect of ketone body oxidation on the transport of glucose into brain cells needs to be studied. Nevertheless, it is the author's view that the mechanism is likely to be broadly similar to that in muscle, but that details such as the mechanism of citrate accumulation may be different.

In the postabsorptive state the kidney cortex uses about 34 g of glucose per day. However, it can be calculated that glucose production via gluconeogenesis during starvation is only sufficient to meet the glucose requirement of the brain and the anaerobic tissues such as red blood cells which obtain their energy from the conversion of glucose to lactate. Hence it is necessary for the kidney cortex to oxidize alternative fuels to glucose during starvation. It has been shown that kidney cortex slices oxidize fatty acids and ketone bodies and that this leads to an increase in the concentration of citrate and a consequent inhibition of phosphofructokinase activity and glucose utilization. Recent work has demonstrated that the small intestine also oxidizes ketone bodies during starvation and that this inhibits glucose oxidation in this tissue. A reduction in the rate of glucose utilization by the small intestine during starvation has also been observed, but this effect is apparently not dependent upon the accumulation of citrate but rather upon a decrease in the concentration of the glycolytic enzymes hexokinase, phosphofructokinase and pyruvate kinase (Hanson and Parsons, 1978). Hence the ability of ketone bodies to act as an alternative fuel to glucose in tissues such as the brain, the kidney cortex and the small intestine will contribute towards the conservation of glucose in conditions such as starvation when the ketone body concentration in the blood increases.

The quantitative estimates of glucose production and utilization by various tissues referred to above are based on arterio–venous difference measurements. A fuller discussion of these estimates and their relation to starvation in man will be found in Cahill (1976).

The regulation of ketogenesis

The synthesis of the ketone bodies acetoacetate and 3-hydroxybutyrate from fatty acids involves the co-operation of two tissues, namely adipose tissue and the liver. Fatty acids are first mobilized from adipose tissue then taken up by the liver and finally converted into ketone bodies. Regulation of ketogenesis, therefore, involves control of fatty acid mobilization in adipose tissue and of the conversion of fatty acids into ketone bodies in the liver. Furthermore, the metabolism of these two tissues must be integrated to ensure that the capacity for ketone body synthesis in the liver is matched by the rate of supply of fatty acids from adipose tissue. The control of fatty acid mobilization has already been discussed in a previous section and hence only factors which act at the level of the liver and which integrate the metabolism of the two tissues will be discussed in this section.

Fatty acids taken up from the blood by the liver are first esterified to CoA in an ATP-dependent reaction. The resultant cytoplasmic fatty acyl-CoA may either be esterified with glycerol-3-phosphate to form triacylglycerol or be esterified with carnitine and transported as fatty acyl-carnitine into the mitochondrion which is the site of ketone body synthesis. Once inside the mitochondrion, fatty acyl-carnitine is converted back to fatty acyl-CoA which undergoes β-oxidation to form acetyl-CoA. If ketogenesis is to occur, then this branch point of metabolism must be regulated so that fatty acyl-CoA is directed towards the mitochondrion. Regulation of this branch point could, therefore, in principle involve inhibition of triacylglycerol synthesis, stimulation of transport of fatty acid residues into the mitochondrion or a combination of both processes. Mitochondrial acetyl-CoA may be metabolized either via the tricarboxylic acid cycle to form carbon dioxide or via the HMG-CoA pathway to form ketone bodies. If ketogenesis is to occur then mitochondrial acetyl-CoA must be directed towards the HMG-CoA pathway. Hence, in principle, regulation of this branch point could involve inhibition of the tricarboxylic cycle, stimulation of the HMG-CoA pathway or a combination of both processes. The pathways described above and their relationship to one another are presented in figure 1.

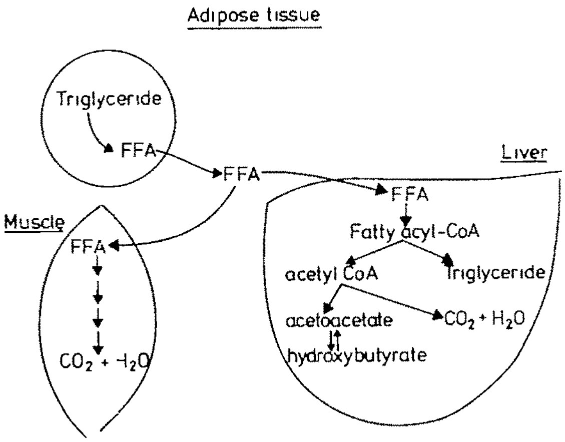

FIG. 1. Pathways of fatty acid oxidation and esterification in the liver.

The regulation of ketogenesis in the liver has been studied using *in vitro* preparations of this tissue, in particular the perfused rat liver and isolated rat hepatocytes. When livers from fed, starved and diabetic rats were perfused with the same concentration of oleic acid it was found that, despite similar rates of uptake of this long chain fatty acid by all three livers, the rates of ketogenesis in the livers from starved and diabetic animals were very much greater. This finding implies that the greater rates of fatty acid mobilization characteristic of the starved and diabetic states are not alone sufficient to ensure high rates of ketogenesis. Hence control mechanisms must exist in the liver to ensure that in the starved and diabetic states fatty acids are directed towards the ketogenic pathway.

Octanoate, a medium chain fatty acid, can cross the inner membrane without prior esterification to carnitine. The finding that octanoate is oxidized at similar rates by perfused liver from fed, starved and diabetic rats suggests that the transport of fatty acid residues across the inner mitochondrial membrane may regulate the distribution of fatty acyl-CoA between mitochondrion and cytoplasm. It is thought that the membrane-bound enzyme carnitine acyl transferase-I catalyses the rate-limiting step in the transport of fatty acid residues into the mitochondrion. Furthermore, the results also suggest that transport of fatty acid residues into the mitochondrion is less rapid in the livers from fed rats and more rapid in the livers from starved and diabetic rats thus allowing greater rates of ketogenesis in the starved and diabetic state.

These observations focused attention on the regulation of carnitine acyl transferase-I activity as a means of activating the pathway for the oxidation of fatty acyl-CoA in starvation and diabetes. A large number of intermediates of glucose and fatty acid metabolism were tested for their ability to activate or inhibit this enzyme. As a result it was discovered that physiological concentrations of malonyl-CoA inhibited carnitine acyl transferase-I activity. Malonyl-CoA is the first intermediate unique to the pathway of fatty acid synthesis. Hence, when the rate of fatty acid synthesis in the liver is high and the malonyl-CoA concentration is high, carnitine acyl transferase-I activity will be inhibited and consequently the rate of fatty acid oxidation and ketogenesis will be low. Hence the role of malonyl-CoA as an inhibitor of carnitine acyl transferase-I and as an intermediate of the pathway of fatty acid synthesis allows reciprocal control of fatty acid oxidation and synthesis in the liver. It has been shown that rates of fatty acid synthesis and oxidation, when measured simultaneously in isolated rat hepatocytes are related in a linear and reciprocal fashion.

Glucagon stimulates the rate of ketogenesis in the liver. This effect may be partly a result of the ability of glucagon to decrease the malonyl-CoA concentration. The activity of the enzyme acetyl-CoA carboxylase controls the rate of malonyl-CoA synthesis in the liver, while the activity of the fatty acid synthetase enzyme complex controls the rate of its utilization. Hence it might be expected that glucagon decreases the malonyl-CoA concentration by changing the activities of one or both of these enzymes. It has recently been shown that impure preparations of acetyl-CoA carboxylase are phosphorylated by cAMP-dependent protein kinase—a process that is accompanied by inhibition of the enzyme (Kim, 1979). Hence glucagon can inhibit acetyl-CoA carboxylase since it increases cAMP concentration and consequently activates cAMP-dependent protein kinase. Inhibition of acetyl-CoA carboxylase by glucagon will reduce the rate of malonyl-CoA synthesis and hence decrease the malonyl-CoA concentration. As a result carnitine acyl transferase-I will be de-inhibited and the rate of ketogenesis will increase.

It is not clear at the present time how far inhibition of the rate of fatty acid esterification during starvation and diabetes contributes to increased rates of ketogenesis in these situations. Nevertheless, it is likely that some control mechanism ensures that the rate of fatty acid esterification is inhibited in ketotic states otherwise de-inhibition of fatty acid oxidation and ketogenesis when the malonyl-CoA concentration decreases would not necessarily direct fatty acyl-CoA into the oxidative pathway but merely allow competition between the oxidative and esterification pathways for the available fatty acyl-CoA.

A second problem concerning the regulation of ketogenesis is the nature of the factors which control the distribution of mitochondrial acetyl-CoA between the tricarboxylic acid cycle and the HMG-CoA pathway. No increase in the capacity of the HMG-CoA pathway in ketotic states has been detected. It has been shown that the capacity of the tricarboxylic acid cycle decreases during ketogenesis, but this effect is not essential for enhanced ketogenesis. The mechanism of regulation of this branch point in metabolism remains to be established. Factors which integrate the mobilization of fatty acids from adipose tissue and the synthesis of ketone bodies from fatty acids in the liver include the concentration of circulating insulin, glucagon and ketone bodies. During starvation the concentration of insulin in the blood decreases while that of glucagon increases. Enhanced ketogenesis during starvation is caused by a simultaneous increase in the rate of fatty acid mobilization from adipose tissue and an increased capacity for ketone body synthesis from fatty acids in the liver. The former is probably mediated by a decline in the concentration of the antilipolytic hormone insulin, while the latter is probably mediated by an increase in the concentration of the ketogenic hormone glucagon. However, the author considers that this kind of hormonal regulation alone may not be sufficiently precise to ensure that the rate of supply of fatty acids from adipose tissue is precisely matched to the rate of their utilization by the liver. Hence a further control mechanism which involves ketone bodies is necessary.

It has been shown that high concentrations of the ketone body 3-hydroxybutyrate stimulate the secretion of the antilipolytic hormone insulin. Furthermore, it has also been shown that 3-hydroxybutyrate directly inhibits the rate of mobilization of fatty acids from adipose tissue and increases the sensitivity of adipose tissue to the effects of insulin (Green and Newsholme, 1979). These are examples of the role of ketone bodies as a metabolic signal. These effects could form the basis of a sensitive feedback control mechanism for regulating the rate of release of fatty acids from adipose tissue in relation to the rate of ketone body synthesis in the liver. Indirect evidence for this control mechanism is provided by the phenomenon of post-exercise ketosis. Immediately after exercise has finished the rate of utilization of fatty acids by muscle will rapidly decrease while the rate of fatty acid mobilization from adipose tissue will remain unchanged. Consequently, the concentration of fatty acids in the blood will increase. This in turn will stimulate the rate of ketogenesis in the liver and hence the ketone body concentration will increase. The antilipolytic action of ketone bodies will ensure that fatty acid mobilization is inhibited so that it now exactly matches the new low rate of fatty acid utilization by muscle. Hence a new metabolic steady state is achieved.

A more detailed discussion of the regulation of ketone body synthesis will be found in McGarry and Foster (1980).

The glucose–fatty acid–ketone body cycle

The glucose–fatty acid cycle can now be extended to include the role of ketone bodies as respiratory substrates and the role of 3–hydroxybutyrate as a metabolic signal. The glucose–fatty acid–ketone body cycle is presented in figure 2. This extended cycle provides a more complete picture of the whole animal's response to conditions of carbohydrate deprivation such as starvation. The role of ketone bodies as respiratory substrates provides an explanation for the inhibition of glucose oxidation and utilization via the glycolytic pathway in the brain and kidney cortex and of glucose oxidation in the small intestine during starvation. Hence, the ability of these tissues to oxidize ketone bodies in preference to glucose in response to an increased ketone body concentration in the blood contributes towards the conservation of glucose during conditions of carbohydrate deprivation. In the case of the brain, inhibition of glucose utilization also allows vital muscle protein to be conserved since this protein is the ultimate source of the glucose used by the brain. The ability of 3-hydroxybutyrate to inhibit lipolysis in adipose tissue forms the basis of a sensitive feedback control mechanism for fatty acid mobilization. Thus the rate of fatty acid mobilization can be regulated, through the 3-hydroxybutyrate concentration in the blood, in relation to the plasma fatty acid concentration and hence to the rate of fatty acid utilization. Furthermore, the inhibitory effect of 3-hydroxybutyrate on lipolysis provides a mechanism for integrating the rate of supply of fatty acids from adipose tissue and the rate of their conversion into ketone bodies in the liver. Further details of the glucose–fatty acid–ketone body cycle are provided by Newsholme (1976).

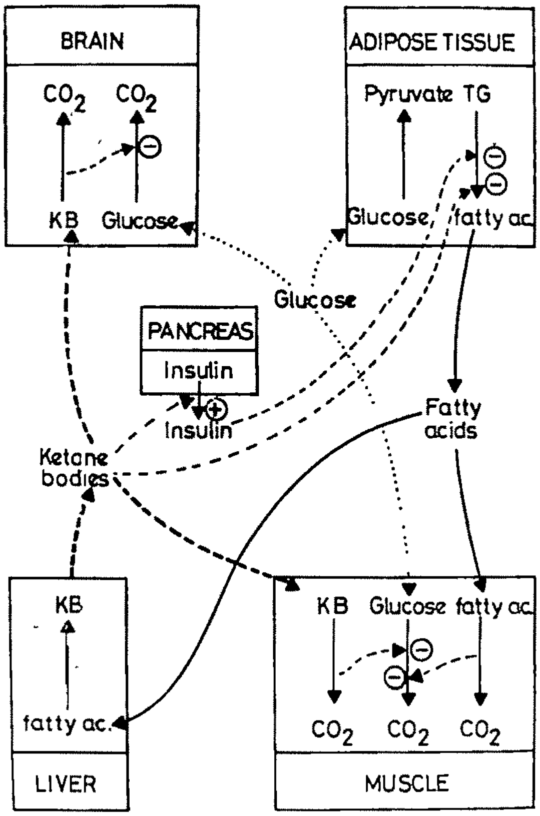

FIG. 2. The glucose–fatty acid–ketone body cycle.

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THE REGULATION OF GLUCOSE PRODUCTION

The role of liver glycogen and gluconeogenesis in the liver and kidney cortex

J. C. STANLEY

In the previous two articles biochemical mechanisms for inhibiting the rate of glucose utilization in muscle, brain, kidney cortex and the small intestine were described. These mechanisms depend upon the availability of fatty acids and ketone bodies in the blood which can be oxidized by these tissues in preference to glucose. Hence, one mechanism for conserving glucose in conditions of carbohydrate deprivation involves the inhibition of glucose utilization. However, some tissues respond to conditions of carbohydrate deprivation by increasing the rate of glucose production from endogenous sources. In the first instance liver glycogen is degraded to provide glucose which is then released into the blood. Following the depletion of the liver glycogen stores, glucose is synthesized via the pathway of gluconeogenesis which is present in the liver and kidney cortex, from precursors such as lactate, glycerol and amino acids (notably alanine and glutamine). Hence the whole animal's response to conditions of carbohydrate deprivation is a combination of reduced glucose utilization and increased glucose production.

Several aspects of the regulation of glucose production are discussed in this article. First, the regulation of glycogen metabolism in the liver is described. Next, some quantitative aspects of glucose production via the gluconeogenic pathway are discussed. This is followed by a description of the regulation of gluconeogenesis in the liver and factors which control the rate of supply of the key gluconeogenic precursor, alanine, from muscle. In addition the role of ketone bodies in the integration of muscle and liver metabolism with regard to glucose synthesis from alanine, and brain metabolism with regard to the utilization of this alanine-derived glucose is discussed. Finally, some aspects of the integration of glutamine metabolism are described with particular reference to the role of this amino acid in starvation and acidosis and the part played by muscle, kidney cortex and the small intestine in its metabolism.

Regulation of glycogen metabolism in the liver by the blood glucose concentration and by hormones

The liver plays an important role in blood glucose homeostasis. When the concentration of glucose in the hepatic portal vein is high (for example after a high carbohydrate meal) the liver removes glucose from the blood. Conversely, when the concentration of glucose in the hepatic portal vein is low (such as during starvation) the liver releases glucose into the blood. Furthermore, the rate of uptake or release of glucose by the liver is proportional to the degree of hyper- or hypoglycaemia. Hence the blood glucose concentration itself can determine whether the liver is a glucose-producing or a glucose-using organ and at what rate glucose is released or taken up by this tissue (Soskin et al., 1938). It is now possible to give some explanation of these properties of the liver at a biochemical level in relation to the regulatory properties of the enzymes which catalyse key reactions in the pathways of glycogen synthesis and degradation.

The transport of glucose across the liver cell membrane is very rapid. As a result the glucose concentration in the liver cell closely follows that in the blood. Therefore, when the concentration of blood glucose increases after a high carbohydrate meal this will be accompanied by an increase in the glucose concentration within the liver cell and when the concentration of blood glucose decreases during starvation this will be accompanied by a decrease in the glucose concentration within the liver cell.

The first step in the synthesis of glycogen from glucose in the liver is phosphorylation of glucose to glucose-6-phosphate, catalysed by glucokinase. This enzyme has a low affinity for glucose and as a result is never saturated by physiological concen-

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trations of glucose. Furthermore, glucokinase in the liver, unlike hexokinase in muscle, is not inhibited by its product glucose-6-phosphate. These two properties of glucokinase ensure that when the concentration of glucose in the liver cell is high then the activity of glucokinase and hence the rate of glucose phosphorylation will be high. Glucose-6-phosphate is converted into glucose-1-phosphate by the enzyme phosphoglucomutase and glucose-1-phosphate is then converted into UDP-glucose by the enzyme UDP-glucose pyrophosphorylase. Finally, the enzyme glycogen synthase uses UDP-glucose units to synthesize the chains of glucose residues which make up the glycogen molecule. It is thought that the activity of glycogen synthase determines the rate of glycogen synthesis in the liver. The regulatory properties of glycogen synthase are crucial to the mechanisms whereby the blood glucose concentration and circulating hormones regulate the rate of glycogen synthesis in the liver.

In the liver, glycogen is degraded to glucose-1-phosphate, one glucose residue at a time, in a reaction catalysed by the enzyme glycogen phosphorylase. Glucose-1-phosphate is then converted to glucose-6-phosphate by phosphoglucomutase and finally the glucose-6-phosphate is hydrolysed to glucose by the enzyme glucose-6-phosphatase. It is the presence of glucose-6-phosphatase in the liver which enables this tissue to produce glucose from glucose-6-phosphate derived from either glycogen breakdown or gluconeogenesis. It is thought that the activity of glycogen phosphorylase determines the rate of glycogen breakdown in the liver. The regulatory properties of glycogen phosphorylase are crucial to the mechanisms whereby the blood glucose concentration and circulating hormones regulate the rate of glycogen breakdown in the liver.

Glycogen phosphorylase exists in two forms, namely glycogen phosphorylase a, which is more catalytically active, and glycogen phosphorylase b, which is less catalytically active. These two forms are interconvertible through two separate reactions catalysed by two separate enzymes; glycogen phosphorylase b is phosphorylated to form glycogen phosphorylase a and the reaction is catalysed by the enzyme phosphorylase b kinase. This interconversion represents activation of glycogen phosphorylase. Glycogen phosphorylase a can be dephosphorylated to reform glycogen phosphorylase b. This reaction is catalysed by the enzyme phosphorylase a phosphatase and, therefore, represents inactivation of glycogen phosphorylase. Hence the rate of glycogen degradation will be determined by the proportion of phosphorylase in the a form, which will be determined by the activities of the two interconverting enzymes, phosphorylase b kinase and phosphorylase a phosphatase. Hence it is the activities of these two latter enzymes that regulate the rate of glycogen breakdown.

Phosphorylase b kinase activity is also regulated by phosphorylation and dephosphorylation. Phosphorylation of the enzyme is catalysed by cAMP-dependent protein kinase and results in the activation of phosphorylase b kinase. As a result, glycogen phosphorylase activity is stimulated and the rate of glycogen breakdown increases. Hence hormones such as glucagon which increase the cAMP concentration in the liver stimulate the rate of glycogen breakdown in this tissue.

Glycogen synthase also exists in two forms, namely glycogen synthase a, which is more catalytically active, and glycogen synthase b, which is less catalytically active. The two forms are interconvertible through the action of two enzymes. Thus glycogen synthase a can be phosphorylated to form glycogen synthase b. This reaction is catalysed by the enzyme cAMP-dependent protein kinase and, therefore, represents inactivation of glycogen synthase. Hence hormones such as glucagon which increase the cAMP concentration in the liver inhibit glycogen synthase activity and decrease the rate of glycogen synthesis. Thus glucagon controls the rate of glycogen synthesis and degradation in the liver in a reciprocal manner. Glycogen synthase b can be dephosphorylated to reform glycogen synthase a. This reaction is catalysed by the enzyme synthase b phosphatase and, therefore, represents activation of glycogen synthase. Hence, the phosphorylated form of glycogen synthase is the less catalytically active, while the phosphorylated form of glycogen phosphorylase is the more catalytically active. The various enzymatic interconversions described above are summarized in figure 1.

The blood glucose concentration exerts reciprocal control over the rates of both synthesis and degradation of glycogen in the liver. The following mechanism was established by studies of the *in vitro* kinetic properties of purified enzymes of liver glycogen metabolism and their interconverting enzymes and was subsequently confirmed *in vivo*.

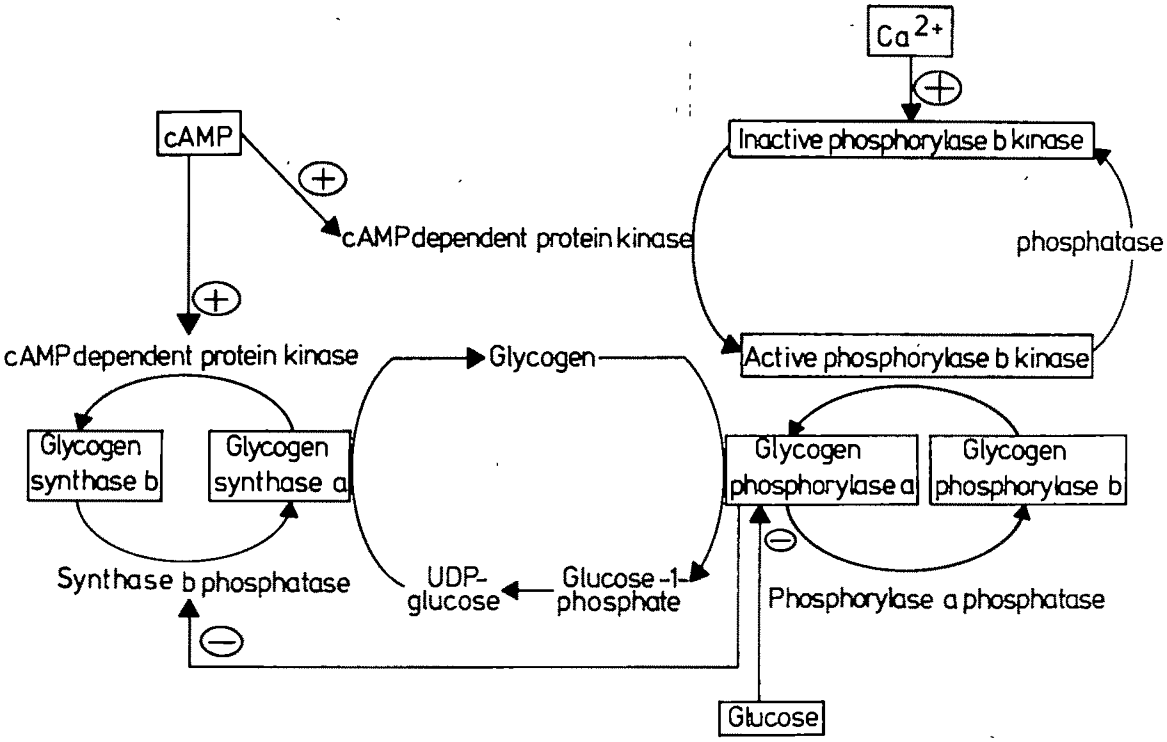

FIG. 1. Regulation of glycogen phosphorylase and glycogen synthase in the liver by phosphorylation and dephosphorylation.

When the blood glucose concentration increases this is accompanied by an increase in the glucose concentration in the liver cell. Glucose binds directly to glycogen phosphorylase a, which as a result becomes a better substrate for phosphorylase a phosphatase. Hence the rate of dephosphorylation of glycogen phosphorylase increases and the concentration of glycogen phosphorylase a in the liver cell declines. As a result the rate of glycogen degradation in the liver decreases and the rate of release of glucose by the liver decreases.

The activity of synthase b phosphatase is inhibited by high concentrations of glycogen phosphorylase a. However, once the concentration of glycogen phosphorylase a decreases to less than 10% of the total glycogen phosphorylase concentration in the liver cell then synthase b phosphatase is deinhibited. Hence the rate of dephosphorylation of glycogen synthase increases, leading to an increase in its activity. As a result the rate of glycogen synthesis in the liver increases and the rate of uptake of glucose by the liver increases. This sequence of events is reversed when the blood glucose concentration decreases and hence provides a mechanism for controlling rates of glycogen synthesis and degradation in the liver in response to the blood glucose concentration. A more detailed discussion of this mechanism has been given by Stalmans (1976).

However, a variety of hormones also have the ability to regulate the enzyme interconversions mentioned above. Thus glucagon and β-adrenergic agonists stimulate the activity of adenyl cyclase and hence increase the concentration of cAMP within the liver cell. As a result the activity of cAMP-dependent protein kinase increases. This enzyme phosphorylates glycogen synthase a, converting it to glycogen synthase b and as a result the activity of this enzyme decreases, causing a decrease in the rate of glycogen synthesis. In addition, cAMP-dependent protein kinase phosphorylates phosphorylase b kinase and hence converts it to a more active form. Phosphorylase b kinase then phosphorylates phosphorylase b to phosphorylase a. As a result the activity of glycogen phosphorylase increases, causing an increase in the rate of glycogen degradation. Hence glucagon and β-adrenergic agonists stimulate glucose production from glycogen in the liver.

Not all hormones regulate glycogen metabolism in the liver via changes in the cAMP concentration. Thus α-adrenergic agonists, vasopressin, oxytocin and angiotensin II stimulate the rate of glycogen degradation in the liver without altering the cAMP concentration. It is thought that one possible mechanism of action for these hormones involves an increase in the Ca^{2-} concentration in the cytoplasm of the liver cell. One source of Ca^{2+} may be the mitochondria. Phosphorylase b kinase is stimulated by Ca^{2+} and hence the rate of conversion of phosphorylase b to phosphorylase a increases and the rate of glycogen degradation also increases. Many of the details of this mechanism remain to be discovered, in particular the mechanism whereby the hormones stimulate the transfer of Ca^{2+} from mitochondria to cytoplasm.

Insulin antagonizes the action of all the hormones mentioned above. Very little is known about the mechanism of action of insulin. However, it is known that insulin inactivates glycogen phosphorylase and. phosphorylase b kinase. One attractive possibility is that insulin stimulates the activity of one or more of the protein phosphatases.

A more detailed discussion of the hormonal regulation of glycogen metabolism in the liver has been given by Hems and Whitton (1980).

Quantitative aspects of glucose production via the gluconeogenic pathway

When liver glycogen stores are exhausted by starvation or prolonged exercise the only remaining endogenous source of glucose is gluconeogenesis. This pathway for the synthesis of glucose is present in the liver and the kidney cortex. The major precursors for gluconeogenesis are lactate, glycerol and certain amino acids. In the case of the liver the amino acid alanine is the major gluconeogenic precursor while in the kidney cortex the amino acid glutamine is an important precursor. In resting human subjects lactate is derived from the anaerobic tissues such as red blood cells, white blood cells, kidney medulla and testis while in exercising human subjects lactate may also be derived from the anaerobic respiration of glucose in muscle. Glycerol is derived from lipolysis in adipose tissue and alanine and glutamine are released by muscle following protein degradation in this tissue. Hence efficient synthesis of glucose in conditions of carbohydrate deprivation requires the integration of metabolism in those tisues which supply gluconeogenic precursors with the metabolism in those tissues which use the precursors for glucose synthesis. Some possible mechanisms for achieving this are discussed in relation to alanine in a later section. Furthermore, regulatory mechanisms must exist to stimulate the rate of gluconeogenesis in conditions of carbohydrate deprivation in order to satisfy the demands of tissues which continue to use glucose in these circumstances. Some of these mechanisms are also discussed below. Some quantitative aspects of glucose production via the gluconeogenic pathway are discussed in this section.

The anaerobic tissues require approximately 40 g of glucose per day. Since these tissues cannot derive energy from any other source, this requirement for glucose must be met even during prolonged starvation. The lactate released by the anaerboic tissues is taken up by the liver and converted into glucose via the gluconeogenic pathway. The glucose is then released by the liver and taken up again by the anaerboic tissues and converted back to lactate via the glycolytic pathway. The energy required for the resynthesis of glucose from lactate in the liver is provided by fatty acid oxidation and hence this cycle maintains the supply of glucose to the anaerobic tissues at the expense of fatty acids.

In the early stages of starvation, the brain uses about 120 g of glucose per day. Once the liver glycogen stores are exhausted this glucose must be provided by gluconeogenesis. It has been calculated that the glycerol released by adipose tissue in resting human subjects is sufficient to support the synthesis of about 20 g of glucose per day. The remaining 100 g per day must, therefore, be derived from amino acids such as alanine and glutamine and hence ultimately from protein degradation in muscle. However, as has already been pointed out, as starvation proceeds the glucose requirement of the brain decreases to about 35 g per day because ketone bodies are being oxidized in preference to glucose by the brain. As a result amino acids and hence protein degradation in muscle need only supply about 15 g of glucose after prolonged starvation, thus allowing the conservation of muscle protein. It follows that the decline in the rate of gluconeogenesis from amino acid precursors must occur in parallel with the decline in the rate of glucose utilization by the brain. One possible mechanism for integrating the metabolism of these two tissues is suggested below. For the moment, however, it may be stated that the decrease in the rate of gluconeogenesis from amino acids during prolonged starvation is mainly the result of a decreased rate of hepatic gluconeogenesis from alanine. As a result, as starvation proceeds the relative importance of the liver as a gluconeogenic organ declines while that of the kidney cortex increases. It should be pointed out that gluconeogenesis from either glycerol or amino acids represents a gain of carbohydrate for the body, unlike gluconeogenesis from lactate, which merely involves the recycling of carbohydrate.

Regulation of gluconeogenesis in the liver

The gluconeogenic precursors alanine, lactate and glycerol can all be converted into intermediates of the gluconeogenic pathway. Both alanine and lactate are converted into pyruvate, while glycerol is converted into triose phosphate. The gluconeogenic pathway involves the conversion of pyruvate into glucose and hence is the reverse of the glycolytic pathway. Both pathways share enzyme-catalysed reactions which are maintained close to equilibrium *in vivo*. However, the enzyme-catalysed reactions which are maintained far from equilibrium *in vivo* are unique to either the glycolytic or the gluconeogenic pathway.

The activities of the enzymes unique to either the glycolytic or the gluconeogenic pathways oppose each other at three points. The phosphorylation of glucose catalysed by glucokinase in the glycolytic pathway is opposed by the hydrolysis of glucose-6-phosphate catalysed by glucose-6-phosphatase in the gluconeogenic pathway. The phosphorylation of fructose-6-phosphate in the glycolytic pathway catalysed by phosphofructokinase is opposed by the hydrolysis of fructose-1,6-diphosphate catalysed by fructose-1,6-diphosphatase in the gluconeogenic pathway. Finally, the dephosphorylation of phosphoenolpyruvate catalysed by pyruvate kinase in the glycolytic pathway is opposed by several reactions in the gluconeogenic pathway. First, pyruvate is carboxylated to form oxaloacetate in the mitochondrion in a reaction catalysed by pyruvate carboxylase. In the case of those species which possess cytoplasmic phosphoenolpyruvate carboxykinase this is followed by transport of oxaloacetate out of the mitochondrion, indirectly as either malate or aspartate. Oxaloacetate is then reformed in the cytoplasm and finally decarboxylated and phosphorylated by the enzyme phosphoenolpyruvate carboxykinase to form phosphoenolpyruvate. It should be emphasized that the activities of the enzymes unique to either glycolysis or gluconeogenesis oppose each other only as far as the pathway intermediates are concerned. When the enzyme-catalysed reactions as a whole are compared, it can be seen that they are not simply the reverse of one another.

It has been shown that the enzymes unique to either glycolysis or gluconeogenesis are simultaneously catalytically active in the liver cell. This has two major consequences for the regulation of gluconeogenesis in the liver. First, enzymes such as phosphofructokinase and fructose-1,6-diphosphatase, the activities of which oppose one another, catalyse substrate cycles and as a result the sensitivity of such enzyme-catalysed reactions to changes in the concentration of regulator molecules is increased. Second, changes in the rate of gluconeogenesis can be brought about not only by changes in the activities of the enzymes unique to gluconeogenesis, but also by changes in the activities of enzymes unique to glycolysis. For example, the hydrolysis of fructose-1,6-diphosphate in the gluconeogenic pathway can be stimulated not only by an increase in the activity of fructose-1,6-diphosphatase, but also by a decrease in the activity of phosphofructokinase. Furthermore, a combination of both effects could be involved. Hence the enzymes which catalyse the three substrate cycles in the gluconeogenic and glycolytic pathways are logical control sites.

The rate of gluconeogenesis in the liver is stimulated by glucagon, catecholamines and glucocorticoids and inhibited by insulin. Thus, during starvation when the insulin concentration in the blood decreases and the concentration of glucagon increases, the rate of hepatic gluconeogenesis increases. This mechanism accounts in part for the increased rate of hepatic gluconeogenesis during starvation, but is accompanied by an increase in the rate of supply of the key gluconeogenic precursor alanine from skeletal muscle (see later). As might be expected, the mechanism of action of glucagon on the gluconeogenic pathway is mediated by an increase in the cAMP concentration and an increase in the activity of cAMP-dependent protein kinase. It has recently been shown that the gluconeogenic enzyme fructose-1,6-diphosphatase is phosphorylated by cAMP-dependent protein kinase and activated while the glycolytic enzyme phosphofructokinase is phosphorylated by the same enzyme and inactivated. As a result, the net rate at which fructose-1,6-diphosphate is converted to fructose-6-phosphate is stimulated. The glycolytic enzyme pyruvate kinase is also phosphorylated by cAMP-dependent protein kinase and inactivated. As a result, the net rate at which pyruvate is converted to phosphoenolpyruvate is stimulated. These findings explain in part the ability of glucagon to stimulate the rate of hepatic gluconeogenesis. However, there is no evidence for an effect of glucagon on the activities of either glucokinase or glucose-6-phosphatase and hence on the net rate of conversion of glucose-6-phosphate to glucose. Additional sites of action of glucagon on the hepatic gluconeogenic pathway include the transport of alanine across the liver cell membrane and the transport of pyruvate across the inner mitochondrial membrane.

Catecholamines probably stimulate the rate of gluconeogenesis via cAMP-dependent and cAMP-independent mechanisms. The cAMP-dependent mechanism is presumably similar to that already described above for glucagon. The cAMP-independent mechanism may be mediated via an increase in the cytoplasmic Ca^{2+} concentration and an increase in the activity of phosphorylase b kinase. Some of the enzymes unique to the glycolytic or gluconeogenic pathways may be substrates for phosphorylase b kinase, although evidence for this possibility is at present lacking. Insulin antagonizes the action of both glucagon and catecholamines on hepatic gluconeogenesis, but the mechanism of action of this hormone is not understood. One site of action of glucocorticoids on the gluconeogenic pathway is the enzyme phosphoenolpyruvate carboxykinase. In contrast to the effects of catecholamines, glucagon and insulin on the rate of gluconeogenesis, the effect of glucocorticoids takes longer to develop. This is because glucocorticoids increase the activity of phosphoenolpyruvate carboxykinase by increasing the concentration of this enzyme. The mechanism of this effect involves an increased rate of synthesis of phosphoenolpyruvate carboxykinase protein as a result of an increased rate of synthesis of the mRNA specific for this enzyme. Hence glucocorticoids derepress the gene which codes for phosphoenolpyruvate carboxykinase synthesis. As a result the net rate at which pyruvate is converted to phosphoenolpyruvate is stimulated by glucocorticoids.

The hormonal regulation of gluconeogenesis in the liver has been reviewed recently by Pilkis, Park and Claus (1978).

Alanine synthesis in skeletal muscle

During the early stages of starvation the rate of protein degradation in skeletal muscle is high. This is accompanied by a high rate of release of amino acids into the blood. However, the composition of the mixture of amino acids released by the muscle does not reflect the amino acid composition of muscle protein. Thus, measurements of arteriovenous concentration differences of amino acids across human muscle during starvation show that about 60% of the total amino acid released by muscle is either alanine or glutamine. By contrast, other amino acids such as valine, leucine, isoleucine, glutamate and aspartate are released in smaller amounts than would be expected from the known composition of muscle protein (Felig, 1975). These observations suggest that alanine and glutamine are synthesized in muscle during starvation and that possible sources of the nitrogen and carbon necessary for these syntheses are the other amino acids.

Alanine synthesis in muscle involves the transamination of pyruvate and, therefore, requires a source of pyruvate and a source of amino groups. These amino groups are ultimately derived from those amino acids which are metabolized in muscle such as leucine, isoleucine, valine and glutamate. Therefore, one factor which will control the rate of alanine synthesis will be the rate of supply of amino groups, some of which will ultimately be provided by the transamination of leucine. These considerations have recently prompted research into factors which regulate the rate of leucine degradation in muscle. It has been established that the most likely control point in this pathway is the multienzyme complex α-ketoisocaproate dehydrogenase, which catalyses a reaction analogous to that catalysed by the pyruvate dehydrogenase multienzyme complex. However, such investigations have not progressed far enough for an account of the regulation of leucine degradation and hence of amino group supply to be given at the present time. Nevertheless, it is likely that factors which regulate α-ketoisocaproate dehydrogenase activity will in turn influence the rate of alanine synthesis.

There are two possible sources of pyruvate for alanine synthesis in muscle. In the fed animal, glucose may provide the necessary pyruvate via the pathway of glycolysis. The pyruvate is transaminated to form alanine, which is then released into the blood. The liver takes up the alanine, removes the amino group which is used for urea synthesis and converts the pyruvate to glucose via the pathway of gluconeogenesis. The glucose is then released into the blood and taken up by muscle. This cycle is referred to as the glucose–alanine cycle. It must be emphasized that the cycle as described above does not represent a gain of carbohydrate to the body, but rather recycles carbohydrate. One result of the operation of this cycle is the transfer of amino groups from muscle to the liver, which is the only organ in the body capable of urea synthesis. Hence the function of the glucose–alanine cycle in the fed animal may be to allow the oxidation of amino acids such as leucine in muscle after a high protein meal without the accumulation of toxic ammonia.

During conditions of carbohydrate deprivation, however, the concept of the glucose–alanine cycle must be modified to allow net synthesis of glucose. Hence, in the early stages of starvation, muscle protein must be converted into glucose in order to maintain a supply of about 120 g of glucose to the brain per day. Under these circumstances pyruvate must be derived from the carbon skeletons of other amino acids. Amino acids such as valine, isoleucine, aspartate and glutamate can be degraded via specific pathways to intermediates of the tricarboxylic acid cycle. These intermediates will give rise to oxaloacetate which can be converted into phosphoenolpyruvate by the enzyme phosphoenolpyruvate carboxykinase, which is present in muscle (Newsholme and Williams, 1978). The phosphoenolpyruvate is then converted into pyruvate by the enzyme pyruvate kinase and the pyruvate transaminated to form alanine. Oxidation of pyruvate by muscle is prevented during starvation because the multienzyme complex pyruvate dehydrogenase is inhibited as described earlier. Because this enzyme is inhibited, only those amino acids such as leucine which can be degraded to acetyl-CoA without prior conversion to pyruvate can be oxidized by muscle during starvation.

Integration of alanine production in muscle and alanine utilization in the liver

The rate of glucose synthesis from alanine in the liver is regulated not only by hormones, but also by the rate of supply of alanine from skeletal muscle. This situation arises because the capacity of the liver to synthesize glucose from alanine is never saturated by physiological concentrations of alanine. As a result, the greater the plasma alanine concentration, the greater the rate of gluconeogenesis in the liver. Hence any factor which changes the rate of protein degradation in muscle will also change the rate of glucose production from alanine in the liver. The flux-generating step for gluconeogenesis from alanine in the liver, therefore, may be one of the enzyme-catalysed reactions in muscle concerned with the production of this amino acid. The identity of this flux-generating step remains to be established, but is possibly the protease(s) responsible for the hydrolysis of muscle protein during starvation.

The link between muscle and liver metabolism is provided by the plasma concentration of alanine. In the later stages of starvation when the rate of protein degradation in muscle decreases in order to conserve vital muscle protein, there is a corresponding decrease in the rate of release of alanine from muscle. As a result, the rate of gluconeogenesis from alanine in the liver decreases. A decline in the rate of glucose production by the liver in the later stages of starvation is possible because the brain oxidizes ketone bodies in preference to glucose and hence the demand for glucose decreases. The question arises, therefore, as to the identity of the metabolic signal responsible for reducing the rate of protein degradation in parallel with the decrease in the rate of glucose utilization by the brain.

The role of ketone bodies in integrating the metabolism of muscle, liver and brain during starvation

In the later stages of starvation the rate of glucose utilization by the brain decreases as a result of the oxidation of ketone bodies. This process is accompanied by a decrease in the rate of protein degradation in muscle, a decrease in the plasma alanine concentration and consequently a decrease in the rate of hepatic glucose synthesis. It is important that the decrease in the rate of glucose utilization by the brain is regulated in relation to the decrease in the rate of degradation of muscle protein which is the ultimate source of this glucose. Recent studies suggest that ketone bodies directly inhibit the rate of protein degradation in muscle and the rate of alanine release into the blood. Thus infusion of alanine into patients recovering from surgery increases the plasma ketone body concentration and reduces urinary nitrogen excretion (Hoover et al., 1975). Conversely, infusion of ketone bodies into starving human subjects reduces the plasma alanine concentration and reduces urinary nitrogen excretion (Sherwin, Hendler and Felig, 1975).

This role of ketone bodies as metabolic signals suggests a mechanism whereby the metabolism of muscle, liver and brain can be integrated during starvation. An increase in the blood ketone body concentration such as occurs during starvation will inhibit both the rate of glucose utilization in the brain and the rate of protein degradation in muscle which is the ultimate source of this glucose. The biochemical mechanism of the effect of ketone bodies on the rate of protein degradation in muscle has not been well studied. However, it has been shown that the intracellular concentration of the branched-chain amino acids and in particular of leucine increases the rate of protein synthesis and independently decreases the rate of protein degradation in muscle. Thus, when the intracellular concentration of leucine is high the rate of protein degradation in muscle will be low. One way of increasing the leucine concentration in muscle is to inhibit the rate of its oxidation. It has been shown that ketone bodies inhibit the oxidation of the branched-chain amino acids leucine, isoleucine and valine in muscle. It has already been suggested that the likely point of control in the pathway of leucine oxidation in muscle is the reaction catalysed by the α-ketoisocaproate dehydrogenase multienzyme complex. Hence it is possible that ketone bodies may either directly or indirectly inhibit the activity of this enzyme and in so doing reduce the rate of protein degradation in muscle. Therefore, the regulatory properties of α-ketoisocaproate dehydrogenase may be of crucial importance in mediating the effect of ketone bodies

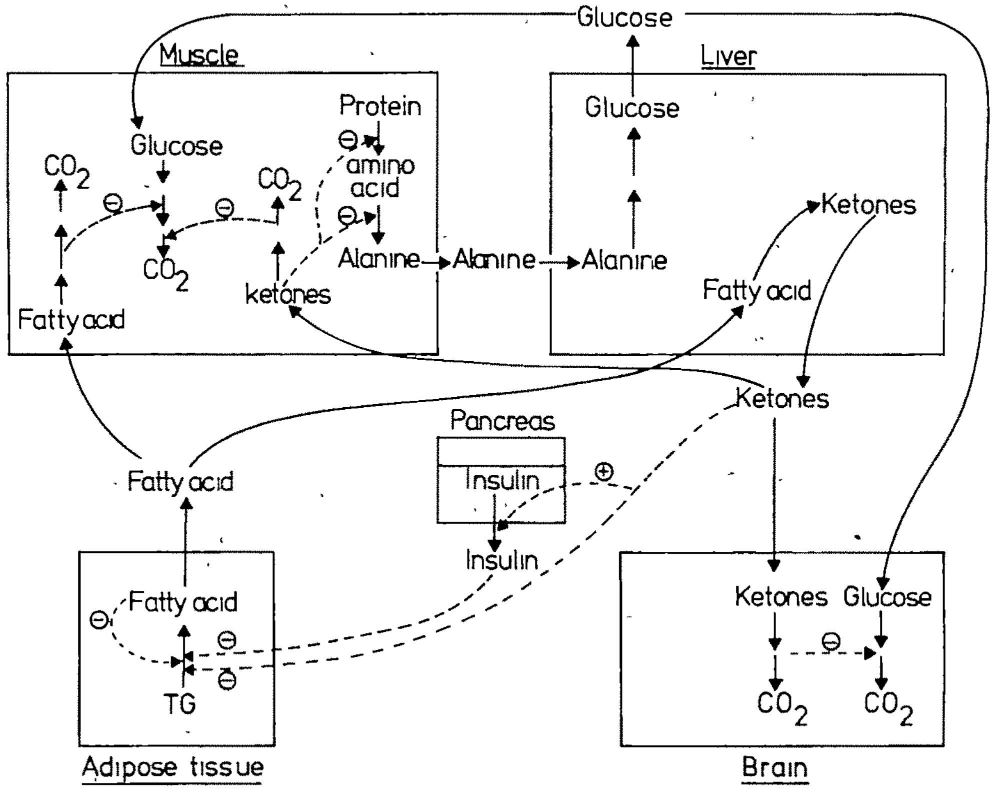

FIG. 2. The role of ketone bodies in the integration of carbohydrate, fat and protein metabolism.

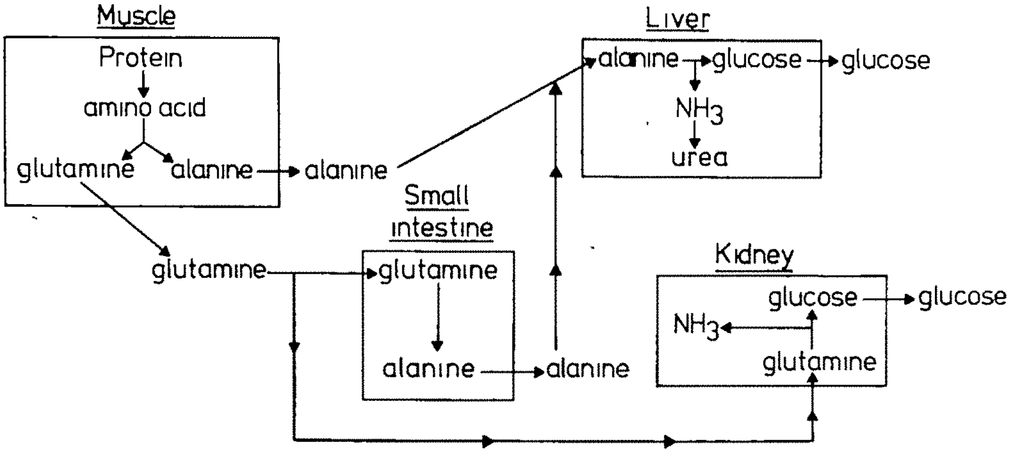

FIG 3. The roles of muscle, small intestine, liver and kidney cortex in the metabolism of alanine and glutamine.

on the rate of protein degradation in muscle. These regulatory properties are currently being studied (Parker and Randle, 1980).

The topics covered in the previous three sections of this article have been discussed recently in more detail by Snell (1980). The role of ketone bodies in the integration of carbohydrate, fat and protein metabolism in the whole animal is illustrated in figure 2.

The physiological significance of glutamine

During starvation glutamine is released by skeletal muscle in larger amounts than would be expected from the known composition of muscle protein (Felig, 1975). This observation implies that muscle synthesizes and releases glutamine during starvation. Glutamine is synthesized from glutamate in a reaction catalysed by the enzyme glutamine synthetase. Glutamate is synthesized by the transamination of α-ketoglutarate, which is in turn derived from the tricarboxylic acid cycle. Net synthesis of α-ketoglutarate can be achieved by condensation of acetyl-CoA and oxaloacetate to form citrate, which is converted to α-ketoglutarate via reactions of the cycle. The ultimate source of this acetyl-CoA and oxaloacetate is the carbon skeletons of amino acids which are metabolized by muscle. Thus the acetyl-CoA could be derived from the degradation of leucine and the oxaloacetate from the degradation of asparate. Both these amino acids are known to be degraded by skeletal muscle. The source of nitrogen for glutamine synthesis in muscle is controversial. However, one suggestion is that the purine nucleotide cycle provides the necessary nitrogen (Lowenstein and Goodman, 1978).

During non-acidotic conditions the glutamine released by skeletal muscle is taken up from the blood by the small intestine. It has recently been shown that circulating glutamine is a major respiratory substrate for the small intestine *in vivo* (Windmueller and Spaeth, 1978). One major end-product of glutamine metabolism in the small intestine is alanine. Hence under non-acidotic conditions some of the glutamine released by skeletal muscle is converted into alanine by the small intestine, released into the blood and then converted into glucose by the liver.

During acidotic conditions such as starvation the glutamine released by skeletal muscle is taken up from the blood by the kidney cortex. In the kidney cortex, glutamine is converted into glutamate in a reaction catalysed by the enzyme glutaminase. The enzyme glutamate dehydrogenase then oxidatively deaminates glutamate to α-ketoglutarate. In both these enzyme-catalysed reactions amino groups are lost as ammonia and the production of ammonia enables the kidney to buffer protons produced in acidotic conditions and hence prevents a decrease in the pH of the urine (Pitts, 1971). The α-ketoglutarate formed from glutamine degradation in the kidney cortex is converted into oxaloacetate, an intermediate of the gluconeogenic pathway, via reactions of the tricarboxylic acid cycle. Hence the carbon skeleton of glutamine is used for glucose synthesis in this tissue during acidotic conditions.

As previously mentioned, the kidney cortex becomes the more important gluconeogenic organ after prolonged starvation since the rate of gluconeogenesis from alanine in the liver decreases. Two possible mechanisms may maintain the supply of glutamine to the kidney cortex during prolonged starvation. First, as starvation proceeds the rate of glutamine uptake by the kidney cortex may progressively increase while the rate of uptake by the small intestine of this amino acid may decrease. Second, the rate of release of glutamine by skeletal muscle, unlike the rate of release of alanine by this tissue, may not be reduced during prolonged starvation. These two possible mechanisms require further study.

The roles of muscle, small intestine, liver and kidney cortex in the metabolism of alanine and glutamine are summarized in figure 3.

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MECHANISMS OF HORMONE ACTION

J. C. STANLEY

Circulating hormones play an important role in regulating the flux through metabolic pathways. In general, hormones regulate either the activity of key enzymes of metabolism or the activity of protein transport systems such as those found in the plasma membrane and in the inner mitochondrial membrane. Little is known about the mechanism of action of hormones on transport systems, so the discussion in this article will be confined to the mechanism of action of hormones on key enzymes of metabolism.

Hormones regulate the activity of key enzymes of metabolism in two ways. Many hormones whose effects on metabolism develop relatively rapidly (for example glucagon or adrenaline) regulate the activities of enzymes via covalent modifications such as the phosphorylation or dephosphorylation of specific serine residues of the enzyme protein. Such alterations in the phosphorylation state of the enzyme are brought about by changes in the activities of either protein kinases which catalyse phosphorylation reactions or phosphoprotein phosphatases which catalyse dephosphorylation reactions. Phosphorylation or dephosphorylation change the kinetic properties of enzymes in one of two ways: either the maximal catalytic activity of the enzyme changes or the affinity of the enzyme for its substrates, activators or inhibitors changes. As a result, the flux through the enzyme-catalysed reaction changes in response to the hormone. It is likely that other covalent modifications such as the adenylation and deadenylation of specific tyrosine residues also occur in mammalian cells, but so far this covalent modification has been studied only with bacterial enzymes.

Other hormones whose effects on metabolism develop relatively slowly (such as steroid hormones or thyroid hormones) regulate the activities of key enzymes of metabolism via changes in the concentration of enzyme protein. Such changes in enzyme concentration are brought about by alterations in either the rate of enzyme synthesis or the rate of enzyme degradation. Changes in the rate of enzyme synthesis could, in principle, be caused either by changes in the rate of mRNA synthesis, that is transcription control, or by changes in the rate of mRNA utilization for protein synthesis, that is translation control. Changes in the rate of an enzyme's degradation may involve alterations in the activity of a specific protease or changes in the susceptibility of the enzyme to proteolysis. All these processes are potential sites of action of hormones.

There are two general mechanisms of hormone action. Some hormones such as glucagon bind to protein receptors which are located on the surface of the target cell membrane. Binding of these hormones to their cell surface receptors causes a change in the concentration of a specific intracellular molecule known as a second messenger which mediates the effects of the hormone on the metabolism of the target cell. Cyclic AMP has been identified as the second messenger for glucagon action on the liver and adrenaline action on muscle. By contrast, the protein receptors for steroid hormones such as glucocorticoids are located in the cytoplasm of the target cell and hence a mechanism must exist to enable the cell to take up the hormone. Binding of steroid hormones to their cytoplasmic receptors is followed by translocation of the complex to the nucleus, which is the site of action of these hormones.

In this article the role of cyclic AMP as the second messenger for glucagon action on the liver and adrenaline action on muscle is described first. Some recent developments in our understanding of the mechanism of action of adrenaline on liver metabolism are then discussed. Next some ideas concerning the mechanism of action of insulin are discussed in relation to the effect of this hormone on the rate of glycogen synthesis in muscle. Finally, the mechanism of action of hormones such

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as glucocorticoids which regulate the concentration of enzymes such as phosphoenolpyruvate carboxykinase and tyrosine aminotransferase is described.

Cyclic AMP and the mechanisms of action of glucagon on liver metabolism and adrenaline on muscle and adipose tissue metabolism

Glucagon regulates the flux through a number of metabolic pathways in the liver. Thus, glucagon stimulates the rates of glycogen breakdown, gluconeogenesis and ketogenesis and inhibits the rates of glycogen synthesis and fatty acid synthesis in this tissue. It seems that many, if not all, of these effects are mediated exclusively by cyclic AMP-dependent phosphorylation mechanisms.

Circulating glucagon binds to a protein receptor on the surface of the liver cell membrane. The resultant hormone–receptor complex then interacts with the membrane-bound enzyme adenylcyclase and activates it. This enzyme converts cytoplasmic ATP into cyclic AMP which is the second messenger for glucagon action. As a result, the binding of glucagon to its receptor increases the cytoplasmic concentration of cyclic AMP.

However, the intracellular concentration of cyclic AMP is not determined solely by the activity of adenyl cyclase. The membrane-bound enzyme phosphodiesterase converts cyclic AMP into AMP and hence, when active, this enzyme will tend to decrease the cytoplasmic cyclic AMP concentration. One factor which increases the activity of phosphodiesterase is insulin. As a result, insulin can decrease cyclic AMP concentrations in the liver previously increased by glucagon though it should be stressed that insulin has no effect on basal cyclic AMP concentrations. This effect of insulin explains in part its ability to antagonize the effects of glucagon on liver metabolism.

An increase in the cytoplasmic cyclic AMP concentration in the liver causes the activation of the enzyme cyclic AMP-dependent protein kinase. This enzyme is a tetramer consisting of two regulatory subunits and two catalytic subunits. When the regulatory subunits are bound to the catalytic subunits the enzyme is inactive. Cyclic AMP binds to the regulatory subunits and causes dissociation of the enzyme to form free catalytic subunits which are catalytically active. Hence, in the presence of cyclic AMP, the catalytic subunit of cyclic AMP-dependent protein kinase can phosphorylate those key enzymes of metabolism which are its substrates using the terminal phosphate group of ATP. Enzymes which are substrates for cyclic AMP-dependent protein kinase are characterized by the possession of a short amino acid sequence which is recognized by the kinase. Other factors may regulate the activity of cyclic AMP-dependent protein kinase, since an inhibitor protein for the kinase has been isolated from liver. Factors which regulate the ability of this protein to inhibit the kinase remain to be identified.

Enzymes which are substrates for cyclic AMP-dependent protein kinase in the liver are constantly being identified. Two key enzymes of glycogen metabolism are phosphorylated by the kinase, namely glycogen synthase, which is inhibited, and phosphorylase b kinase, which is activated, thus explaining the ability of glucagon to inhibit glycogen synthesis and stimulate glycogen degradation. Pyruvate kinase and phosphofructokinase are phosphorylated and inhibited while fructose-1, 6-diphosphatase is phosphorylated and activated. As a result glucagon stimulates the rate of gluconeogenesis in the liver. Two key enzymes of fatty acid synthesis, namely ATP citrate lyase and acetyl-CoA carboxylase, are phosphorylated and inhibited and as a result glucagon inhibits the flux through this pathway. Since there are many other substrates for cyclic AMP-dependent protein kinase in the liver, mechanisms must exist to determine which of these enzymes are preferentially phosphorylated in different physiological conditions. Such mechanisms are currently under investigation.

Adrenaline stimulates the rate of glycogen degradation and inhibits the rate of glycogen synthesis in muscle via cyclic AMP-dependent phosphorylation mechanisms. This contrasts with the mechanism of action of adrenaline on glycogen metabolism in the liver (see next section). In muscle, glycogen synthase and phosphorylase b kinase are again substrates for cyclic AMP-dependent protein kinase, thus explaining the effect of adrenaline on glycogen metabolism in this tissue. In adipose tissue the enzyme triglyceride lipase is phosphorylated by the kinase and activated, thus explaining the ability of adrenaline to stimulate the rate of lipolysis in this tissue.

Further details of cyclic AMP-dependent phosphorylation mechanisms and their relationship to the mechanism of action of adrenaline and glucagon on metabolism can be found in Nimmo and Cohen (1977).

Catecholamines, vasopressin and angiotensin II and Ca^{2+} movements

The catecholamines adrenaline and noradrenaline stimulate the rate of glycogen breakdown in muscle and liver by different mechanisms. In muscle, adrenaline stimulates the activity of adenyl cyclase, increases the concentration of cyclic AMP and activates cyclic AMP-dependent protein kinase. This initiates the series of events described in the previous section, which results in the inhibition of glycogen synthesis and the stimulation of glycogen breakdown in muscle. Furthermore, it has been shown that the effect of adrenaline on glycogen metabolism in muscle is mediated exclusively by this cyclic AMP-dependent mechanism (Dietz et al., 1980). This mechanism for adrenaline action is referred to as the β-adrenergic effect and is initiated by the binding of adrenaline to β receptors located on the surface of the muscle cell membrane.

It has been shown that adrenaline stimulates the rate of glycogen breakdown in the liver by a cyclic AMP-independent mechanism, since compounds such as propranolol, which bind to and block the β receptors, do not interfere with this effect (Sherline, Lynch and Glinsmann, 1972). Adrenaline binds to a second class of receptors, located on the surface of the liver cell membrane, known as α receptors. It has recently become apparent that α-adrenergic effects on the liver are mediated by a Ca^{2+}-dependent mechanism and that other hormones such as vasopressin and angiotensin II also stimulate glycogen breakdown in this tissue by a Ca^{2+}-dependent mechanism.

Adrenaline increases the cytoplasmic Ca^{2+} concentration in the liver cell. Possible sources of Ca^{2+} include the extracellular fluid or intracellular organelles such as the mitochondria or the endoplasmic reticulum. It has been shown that adrenaline stimulates the efflux of Ca^{2+} from intracellular sources and the efflux of Ca^{2+} from the liver cell (Blackmore et al., 1978). Furthermore, recent results suggest that the mitochondria are the most important intracellular source of Ca^{2+} in liver cells, although a role for the endoplasmic reticulum has not been ruled out (Blackmore, Dehaye and Exton, 1979). Hence binding of adrenaline to α receptors on the surface of the liver cell membrane must in some way stimulate the efflux of Ca^{2+} from the mitochondria (see below).

Treatment of liver cells with adrenaline stimulates the phosphorylation of a number of enzymes including glycogen phosphorylase, glycogen synthase and pyruvate kinase (Garrison et al., 1979). This finding explains the ability of adrenaline to stimulate glycogen breakdown, inhibit glycogen synthesis and stimulate the rate of gluconeogenesis in the liver. Since adrenaline acts via a Ca^{2+}-dependent, cyclic AMP-independent mechanism, then a Ca^{2+}-dependent protein kinase must be responsible for these phosphorylations rather than cyclic AMP-dependent protein kinase. Phosphorylase 6 kinase is the best studied example of a Ca^{2+}-dependent protein kinase. However, this enzyme has yet to be purified to homogeneity from liver (Vandenheede, De Wulf and Merlevede, 1979) and as a result no direct evidence exists for the phosphorylation of glycogen phosphorylase, glycogen synthase or pyruvate kinase by phosphorylase b kinase from liver. By contrast, phosphorylase b kinase from skeletal muscle has been purified to homogeneity and its structure determined. It is known that this enzyme contains a δ subunit capable of binding Ca^{2+}. Binding of Ca^{2+} to this regulatory subunit activates phosphorylase b kinase (Shenolikar et al., 1979). The δ subunit is identical to the protein calmodulin, the presence of which confers Ca^{2+} sensitivity on a number of biochemical processes. It is likely that phosphorylase b kinase from liver also contains calmodulin and hence that this enzyme is the Ca^{2+}-dependent protein kinase which mediates α-adrenergic effects on glycogen metabolism and gluconeogenesis in this tissue.

The primary response of the liver cell to the binding of adrenaline to the α receptors remains to be established. Nevertheless, it has been shown that α-adrenergic stimulation of the liver is associated with the breakdown of the phospholipid phosphatidyl inositol (see Michell, Kirk and Billah, 1979). It is likely that the site of phosphatidyl inositol breakdown in the liver cell is the plasma membrane, whereas resynthesis of this phospholipid is associated with the endoplasmic reticulum. The products of phosphatidyl inositol breakdown remain to be precisely characterized, but one of these products is myoinositol 1,2 cyclic phosphate. It has been suggested that this compound is the true second messenger for α-adrenergic effects on the liver, although evidence for this proposal has yet to be provided. However, it has been shown that the increase in the Ca^{2+} concentration in the cytoplasm is secondary to the breakdown of phosphatidyl inositol and that the two events are in some way coupled, although the link between them has yet to be identified. Hence, if myoinositol 1,2 cyclic phosphate is the true second messenger for α-adrenergic effects, then this molecule must in some way stimulate efflux of Ca^{2+} from the mitochondria. It is apparent from the above discussion that more work is needed before the precise mechanism of α-adrenergic effects on liver metabolism is established.

More details of the mechanism of α-adrenergic effects on liver metabolism are given by Exton (1980).

The mechanism of insulin action

Insulin is often spoken of as the major anabolic hormone of the body because it stimulates the synthesis of glycogen, lipids and protein in a number of tissues. Despite a considerable amount of research into the problem, the mechanism of action of insulin on metabolism remains to be established. Nevertheless, a number of mechanisms have been suggested to account for the actions of insulin on metabolism, but none of these are very satisfactory. For a discussion of the various mechanisms suggested, the reader is referred to a recent review by Czech (1977). It is not intended to repeat the information in that review here, but rather to discuss the mechanism of action of insulin in relation to one of the better understood examples of this hormone's effects on metabolism.

Insulin stimulates the rate of glycogen synthesis in skeletal muscle. The site of action of insulin is the enzyme glycogen synthase, which exists in two forms in skeletal muscle, namely a phosphorylated form which is less catalytically active and a dephosphorylated form which is more catalytically active. It has been shown that administration of insulin *in vivo* stimulates the activity of glycogen synthase and that this effect can be explained by dephosphorylation of the enzyme (Roach, Rosell-Perez and Larner, 1977). This finding suggests that insulin either stimulates the activity of a phosphoprotein phosphatase or inhibits the activity of a protein kinase. Available evidence favours the former mechanism.

The identity of the phosphoprotein phosphatase which dephosphorylates glycogen synthase has been established and its regulatory properties studied. A protein has been isolated from skeletal muscle which is phosphorylated by cyclic AMP-dependent protein kinase in response to the administration of adrenaline *in vivo* (Foulkes and Cohen, 1979). When phosphorylated, this protein inhibits the activity of the phosphatase and is therefore referred to as an inhibitor protein. In addition it has been shown that administration of insulin *in vivo* causes the dephosphorylation of the protein (Foulkes, Jefferson and Cohen, 1980). As a result, the protein no longer inhibits the phosphatase, which is therefore able to dephosphorylate glycogen synthase and hence activates this enzyme. It is likely that, *in vivo* this protein is a regulatory subunit of the phosphoprotein phosphatase which has become detached from the phosphatase during its purification from muscle.

Since insulin stimulates the dephosphorylation of the inhibitor protein, a second phosphoprotein phosphatase may be involved in mediating the effects of insulin on glycogen synthase in skeletal muscle. The identity of this second phosphoprotein phosphatase and the nature of the factors which regulate its activity remain to be established. However, it is tempting to speculate that insulin stimulates the activity of this second phosphoprotein phosphatase by changing the intracellular concentration of a small molecule which is the second messenger for insulin action.

Possible mechanisms of action of insulin on glycogen synthesis in skeletal muscle have recently been reviewed by Cohen, Nimmo and Proud (1978).

The regulation of enzyme concentration by hormones

In the liver the amino acid tyrosine is degraded via a specific metabolic pathway to give acetoacetate and fumarate. Since fumarate can be converted into glucose via the pathway of gluconeogenesis, then tyrosine is both a glucogenic and a ketogenic amino acid. The first step in the pathway of tyrosine degradation in the liver is catalysed by the enzyme tyrosine aminotransferase. It is likely that the activity of this enzyme controls the flux through the pathway as a whole. The hormonal regulation of tyrosine aminotransferase concentration has been studied intensively.

Glucagon, insulin and glucocorticoids all increase the concentration of liver tyrosine aminotransferase as measured immunochemically. However, it appears that these hormones may act by different mechanisms. The induction of tyrosine aminotransferase activity by the glucocorticoid dexamethasone is characterized by a 1–2 h lag period and is accompanied by an increase in the rate of synthesis of mRNA specific for the enzyme and in the rate of synthesis of enzyme protein (Olson, Thompson and Granner, 1980). The ability of glucagon to induce tyrosine aminotransferase activity may be dependent upon the simultaneous availability of glucocorticoids. This is the so-called permissive effect of glucocorticoids. It is thought that glucocorticoids act first to increase the concentration of mRNA specific for tyrosine aminotransferase and that the subsequent utilization of this mRNA is controlled by a cyclic AMP- and hence glucagon-sensitive mechanism (Ernest, Chen and Feigelson, 1977). By contrast, it has recently been shown that insulin selectively inhibits the rate of tyrosine aminotransferase degradation in the liver (Spencer et al., 1978).

As previously discussed, the enzyme phosphoenolpyruvate carboxykinase catalyses one of the key reactions of the gluconeogenic pathway. The concentration of this enzyme as measured by immunochemical techniques is regulated by hormones such as glucagon, insulin and glucocorticoids. Thus the glucocorticoid dexamethasone increases the rate of synthesis of phosphoenolpyruvate carboxykinase. By using inhibitors of RNA and protein synthesis, it has been established that glucagon increases the rate of enzyme protein synthesis via changes in the cyclic AMP concentration at a post-transcriptional site. Insulin prevents the increased rate of enzyme protein synthesis in response to glucagon or glucocorticoids (see Gunn et al., 1975, for details). Hence insulin has opposite effects on the rates of synthesis of phosphoenol pyruvate carboxykinase and tyrosine aminotransferase.

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ENDOCRINE AND METABOLIC CHANGES DURING SURGERY: ANAESTHETIC IMPLICATIONS

C. TRAYNOR AND G. M. HALL

Surgical procedures evoke an endocrine response which results in substrate mobilization, a change in metabolism towards catabolism with a negative nitrogen balance and retention of salt and water. The magnitude of this response is proportional to the severity of the operative trauma. Intra-abdominal procedures are associated with a much greater response than body surface surgery (Clarke, 1970; Clarke, Johnston and Sheridan, 1970) and cardiac surgery with cardiopulmonary bypass induces profound hormonal and biochemical changes (Stanley et al., 1979).

There is a vast and often conflicting literature on the hormonal and metabolic response to surgery. The purpose of this short article is not to present a complete review of the subject but rather to provide the necessary background information to enable the results described in more detailed studies to be readily interpreted.

Hormones

The initial response to surgical trauma is an increase in the circulating concentrations of the catabolic hormones such as catecholamines, glucagon and cortisol and a concomitant decrease in plasma concentrations of the anabolic hormones, insulin and testosterone. The plasma concentration of cyclic AMP, the common intracellular second messenger for hormones with β-adrenergic agonist activity, has been shown to increase in proportion to the severity of the surgery (Nistrup Madsen et al., 1976). It is not known precisely which hormones are responsible for this increase in plasma cyclic AMP, but Nistrup Madsen and colleagues (1978) have shown a good correlation between changes in plasma adrenaline and cyclic AMP values.

Catecholamines. There are conflicting opinions on the role of circulating catecholamines as mediators of the metabolic response to surgery. This is a result, at least in part, of the recent introduction of radioenzymatic assay techniques the sensitivity and specificity of which render the older fluorimetric methods obsolete. Plasma catecholamines obtained with the fluorimetric method will not be discussed.

Abdominal surgery produces an increase in plasma noradrenaline and adrenaline values (Halter, Pflug and Porte, 1977), whereas pelvic surgery is associated with an increase in plasma adrenaline alone (Nistrup Madsen et al., 1978; Engquist et al., 1980). It is of interest that in both types of surgery the greatest change in adrenaline values was found after the termination of anaesthesia. Cryer and colleagues (Silverberg et al., 1978; Clutter et al., 1980) have attempted to define the circulating concentrations of catecholamines required to produce metabolic and haemodynamic effects by infusing varying concentrations of these agents into normal subjects. Their results suggest that circulating noradrenaline values during surgery are unlikely to cause any metabolic changes, but this does not exclude the possibility of a localized increase in sympathetic efferent activity. On the other hand, plasma adrenaline concentrations during surgery are similar to those at which changes in heart rate, arterial pressure, blood glycerol, blood lactate and plasma glucose occur.

Another method of assessing the importance of sympathoadrenal stimulation during surgery is to investigate the effects of α- and β-adrenergic blockade. Cooper and others (1980) have recently investigated the effect of β-adrenergic blockade with propranolol during pelvic surgery, and found little effect on the overall metabolic response. This result casts doubt on the relevance of the increases in plasma adrenaline described above. Allison, Tomlin and Chamberlain (1969) examined the

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effects of phentolamine on glucose tolerance during surgery, but failed to observe any beneficial effects of α-adrenergic blockade.

The opinion of Butler and colleagues (1977) that the ideal method of assessing the individual catecholamine response to surgery has yet to be defined, is undoubtedly still valid.

Cortisol and ACTH. The plasma cortisol concentration shows a rapid increase in response to surgical stimulation and remains greater than basal values for a variable time after operation (Lush et al., 1972; Gordon, Scott and Percy Robb, 1973). The magnitude and duration of this increase correlate well with the severity of the surgical trauma. Increased cortisol production is secondary to a preceding increase in ACTH secretion (Oyama and Takiguchi, 1970a), but the plasma ACTH concentration is far greater than that required to produce a maximal adrenocortical response (Thoren, 1974), In addition, the normal pituitary–adrenocortical feedback mechanism is no longer effective as both hormones remain increased simultaneously. The administration of ACTH during surgery produces no further increase in plasma cortisol, and corticosteroid administration in the period after operation does not abolish the ACTH–cortisol response (Thoren, 1974).

The urinary excretion of cortisol metabolites, 17-oxogenic steroids, is increased for 3–4 days after surgery, and values are further increased and excretion prolonged if surgical complications arise. The urinary 17-oxosteroid excretion, derived mainly from adrenal androgens, hardly changes after surgery (Johnston, 1964), but it is not known whether this reflects altered ACTH control or changes in hormonal utilization.

The administration of large doses of hydrocortisone or ACTH to normal subjects is associated with the occurrence of hyperglycaemia, protein degradation, sodium and water retention and potassium loss; that is, many of the features of the metabolic response to surgery. However, the increased cortisol concentrations during surgery are now considered to have a "permissive" effect rather than a direct causative role. For example, the severe hyperglycaemia of upper abdominal and thoracic surgery can be markedly decreased in the presence of a normal adrenocortical response (Bromage, Shibata and Willoughby, 1971). Adrenalectomized patients maintained on constant doses of glucocorticoids develop a negative nitrogen balance after operation (Johnston, 1964), although the effect of steroid replacement on plasma cortisol values was not stated.

Growth hormone has mixed anabolic and catabolic effects. It promotes amino acid and protein synthesis, has lipolytic properties and at high concentration is diabetogenic (Oyama and Takiguchi, 1970b). An increase in plasma growth hormone concentration has been reported during surgery (Carstensen et al., 1972; Hall et al., 1978), but this response is not maintained into the period after operation even after cardiac surgery (Charters, Odell and Thompson, 1969; Brandt et al., 1976a; Brandt et al., 1978). In non-stressful states, growth hormone secretion is suppressed by the administration of glucose and stimulated by hypoglycaemia (Williams, 1968).

Activation of the hypothalamic–anterior pituitary axis is responsible for the increased plasma growth hormone values found during surgery, and the inability of the hyperglycaemia of surgery to modulate hormone secretion is another example of the failure of normal regulatory feedback mechanisms. It is probable that growth hormone has only a minor role in the metabolic changes occurring in surgery since a normal metabolic response to trauma occurs in hypophysectomized patients maintained on steroid replacement therapy (Thoren, 1974).

Glucagon. An increase in the concentration of plasma glucagon occurs in a wide variety of major surgical procedures (Russell, Walker and Bloom, 1975), although Brandt and colleagues (1976a) failed to observe an increase in circulating glucagon values in six patients undergoing abdominal hysterectomy.

Increased plasma glucagon concentrations are also found with other forms of trauma such as burns (Wilmore et al., 1976) and major injuries (Lindsey et al., 1974). Russell, Walker and Bloom (1975) observed that the hyperglucagonaemia persisted for 4 days after gastric surgery and was exacerbated in those patients who developed complications in the period after surgery. However, Foster and colleagues (1980) showed recently that the plasma glucagon had returned to normal values 48 h after major abdominal surgery.

Many factors have been implicated in the control of glucagon secretion (Alberti and Nattrass, 1977), but it is not known which of these are responsible for glucagon release during surgery or, indeed, the contribution made by the hyperglucagonaemia to the substrate mobilization of surgery. Unger and colleagues (1962) showed that a non-stress induced hyperglycaemia produced a decrease in plasma glucagon, a control mechanism that is not operative in the hyperglucagonaemic (or normoglucagonaemic) patient during surgery when the blood glucose is increased.

Insulin. Circulating insulin concentrations are decreased during and immediately following surgery in spite of the co-existing hyperglycaemia (Russell, Walker and Bloom, 1975; Brandt et al., 1976a), but return to normal or greater than normal values during the days following surgery (Russell, Walker and Bloom, 1975). The relationship between insulin and glucagon secretion is complex; initially plasma insulin values decrease, whereas plasma glucagon increases, but in the period after operation both hormones increase in concentration. Allison (1971) has suggested that the inhibition of insulin secretion is primarily a result of predominance of α-adrenergic sympathetic activity. The recent finding of significantly lower insulin values in patients who received β-adrenergic blockade during surgery supports this contention (Cooper et al., 1980).

Thyroid hormones. Thyroid function in the peri-operative period has received considerable attention. Many factors can influence the assessment of changes in circulating thyroid hormones and these include the choice of anaesthetic agent, the methods of hormone estimation and changes in thyroid binding proteins (Thoren, 1974; Brandt et al., 1976b). Plasma triiodothyronine (T3) values decrease during surgery (Brandt et al., 1976b) and remain low into the period after operation (Burr et al., 1975), while plasma thyroxine (T4) concentration remains unchanged. It is likely that this phenomenon is caused by a change in peripheral deiodination of T4 with an increase in the formation of the inactive reverse triiodothyronine (rT3). The significance of the deficiency of circulating T3 in surgical patients is unknown.

Other hormones. Plasma testosterone decreases during surgery and decreases further during the period after operation (Oyama, Aoki and Kudo, 1972), with values remaining less than normal for 4–9 days (Carstensen et al., 1972). Surgery produces a marked increase in circulating prolactin (Brandt et al., 1976a), even during laparoscopy (Cooper, personal communication). The mechanisms of these hormonal changes and their metabolic consequences have yet to be determined.

It is apparent from the above description that it is not possible, at present, to designate one particular hormone as responsible for a specific metabolic change. It is likely that the metabolic response to surgery is the result of the increased activity of all the catabolic hormones in the presence of a reduction of the key anabolic hormone—insulin.

Protein metabolism

An increase in protein degradation is a major effect of the body's response to surgical trauma. The urinary excretion of nitrogen is increased for 4–5 days after abdominal surgery and a man of average build may lose 0.5 kg of lean tissue per day after a major abdominal operation (Johnston, 1964). The duration and magnitude of this nitrogen loss is related to the severity of the surgery and the nutritional status of the patient (Fleck, 1980). Well-nourished patients have a greater nitrogen excretion and it has been suggested that severe nitrogen loss in debilitated patients, who normally tend to conserve their protein, is associated with a poor prognosis (Johnston, 1964).

There is an initial decrease in protein synthesis in muscle (O'Keefe, Sender and James, 1974) followed by an increase in protein catabolism (Gross, Holbrook and Irving, 1978). The main effect of protein degradation is the release of certain amino acids; particularly alanine, for transport to the liver for gluconeogenesis. The deamination in the liver of this increased amino acid flux from the periphery leads to the characteristic increase in urea production and excretion. Elia and colleagues (1980) have demonstrated an augmented uptake of infused alanine during surgery which they suggest may reflect an increase in hepatic gluconeogenesis. Thus in the period after operation when liver glycogen stores have been depleted, muscle protein breakdown ensures the maintenance of the supply of glucose. The hormonal control of muscle proteolysis and gluconeogenesis is complex, but the increased glucagon and cortisol concentrations in the presence of insulin suppression are important factors.

Carbohydrate metabolism

The increase in blood glucose concentration found during surgery is roughly proportional to the severity of the surgical trauma. Glucose values greater than 10 mmol $litre^{-1}$ are not uncommon during cardiac surgery and may cause glycosuria (Brandt et al., 1978). The mechanism of the hyperglycaemic response is complex as the normal neurohormonal regulation of blood glucose is no longer effective. Suppression of insulin secretion is an early response to surgical stimulation and this has lead to studies of glucose utilization in the peri-operative period. Aarimaa and colleagues (1974), using serial i.v. glucose tolerance tests, found that glucose utilization was decreased during surgery, and also in the period after operation when insulin values had returned to normal, suggesting the presence of insulin resistance.

Thus the hyperglycaemia of surgery is the result of an increase in glucose production compared with the rate of utilization, although the relative contributions of increased hepatic glycogenolysis and gluconeogenesis are disputed (Cooper et al., 1980; Richards 1980). It is possible that, after operation, the mobilization of free fatty acids (FFA) contributes to the reduction in glucose utilization (the glucose–FFA cycle), but this is unlikely to be of any importance during surgery because there is little change in circulating FFA values (Hall et al., 1978; Kehlet et al., 1979).

Fat metabolism

The release of FFA from adipose tissue is the result of two opposing processes, lipolysis and lipogenesis. Lipolysis is stimulated by many hormones, but is most sensitive to β-adrenergic stimulation by catecholamines. Lipogenesis, an anabolic process, is controlled by insulin. There is usually little change in fat metabolism during surgery, although Hall and others (1978) observed a decrease in plasma FFA and glycerol values after the induction of anaesthesia and suggested that this was as a result of a reduction in sympathetic activity caused by apprehension before operation. Similarly, Cooper and colleagues (1979) and Kehlet and colleagues (1979) found that extradural analgesia for pelvic surgery was associated with a reduction in plasma FFA and glycerol as a result of efferent sympathetic blockade. The administration of heparin during surgery causes a large and immediate increase in plasma FFA because of stimulation of the enzyme, lipoprotein lipase.

There is no clear pattern to the ketone body response to surgery. For example, Brandt and colleagues (1978) reported a small increase in β-hydroxybutyrate values to 250 μmol $litre^{-1}$ after cardiac surgery, whereas Kehlet and colleagues (1979) recorded concentrations of 2 mmol $litre^{-1}$ following hysterectomy. It is possible that the wide variation in ketone body response to surgery is similar to that observed during starvation (Rich and Whitehouse, 1979).

Salt and water metabolism

Sodium and water retention and potassium loss are amongst the most constant features of the body's response to surgery. About two-thirds of the sodium intake after surgery is retained during the 48 h after major surgery (Menzies Gow and Cochrane, 1979). Plasma ADH (Oyama and Kimura, 1970), aldosterone (Engquist et al., 1978) and renin (Robertson and Michaelis, 1972) concentrations are increased during surgery, but the precise mechanism of the alteration in salt and water balance remains unclear. The increase in adrenocortical activity that accompanies surgery may also be a contributory factor.

There are conflicting reports on the effects of extradural analgesia during surgery on sodium and potassium homeostasis. Bevan (1971) reported less sodium retention in the period after surgery with extradural analgesia, although water retention was unchanged. Brandt, Ølgaard and Kehlet (1979) were unable to confirm these changes in sodium balance in spite of the abolition of the increases in plasma cortisol, renin and aldosterone, although the potassium loss after operation was decreased. Similarly, Menzies Gow and Cochrane (1979) found no effect of extradural analgesia on sodium retention after abdominal surgery, but in their study plasma renin values were higher in the extradural group. Differences in the selection of patients, sodium intake, fluid replacement, arterial pressure and other important variables undoubtedly contributed to these findings.

High-dose fentanyl anaesthesia has been shown to abolish the ADH response to cardiac surgery until the onset of cardiopulmonary bypass, but the effect of ADH-inhibition on water balance in the period after operation has not been studied.

Activation of the response

Afferent nerve impulses from the wound area initiate the hormonal and physiological changes which occur in response to surgery. Hume and Egdahl (1959) demonstrated that the adrenocortical response to an injury of the hind-limb in animals can be abolished by peripheral nerve section, transection of the spinal cord above the injury, or section through the medulla oblongata. Wilmore and colleagues (1976) considered that changes in the afferent neuronal input to the hypothalamic area altered central homeostatic mechanisms with consequent changes in pituitary and autonomic nervous system function. Autonomic as well as somatic afferent fibre activity is important in initiating the response, since analgesia *per se* does not prevent the hormonal changes (Bromage, Shibata and Willoughby, 1971).

In the past there has been considerable speculation about the existence of "wound hormones" which may have a role in eliciting the endocrine and metabolic responses to trauma. The release of prostaglandins, serotonin, acetylcholine and various amino acids from the damaged tissues have all been suggested as possible "wound hormones". The classical experiments of Egdahl (1959) on the isolated dog leg preparation failed to support this concept. However, Wilmore and colleagues (1976) still consider that such substances may have a part to play in burns and severe trauma.

In addition to the increase in afferent neuronal activity from the area of surgery, a variety of other physiological disturbances contribute to the overall hormonal response.

The effects of haemorrhage are well known to the anaesthetist, but partial starvation and dehydration, not uncommon in surgical patients, are probably also important in exacerbating the endocrine changes. Anxiety and fear increase cortisol secretion and cortisol values before operation have been shown to be influenced by premedication and the sleep pattern of the previous night (Oyama, 1973). In the period after operation factors such as infection, prolonged bed rest, hypoxaemia and even alterations in the usual day–night physiological cycles all contribute to the changes in endocrine function.

Modification of the neuroendocrine response to surgery

This may be attempted in two ways. The first method is aimed at the reduction or abolition of the endocrine and metabolic changes that result from surgical stimulation. This may be achieved either by afferent neuronal blockade with local analgesics, for example extradural or spinal analgesia, or by the inhibition of hypothalamic function with large doses of opiates (George et al., 1974). The second approach is to try to minimize the consequences of the altered hormonal environment after this has occurred. This is usually undertaken by the administration, either parenterally or enterally, of appropriate substrates. Other techniques include the infusion of anabolic hormones (particularly insulin) and nursing the patient in a thermoneutral environment.

Extradural analgesia, with or without general anaesthesia, either reduces or abolishes the usual increase in blood glucose and plasma cortisol, growth hormone, adrenaline and cyclic AMP values found during pelvic surgery (Gordon, Scott and Percy Robb, 1973; Kehlet et al; 1979; Engquist et al., 1980). Complete abolition of the cortisol and growth hormone response to pelvic surgery can only be achieved with an extradural block extending from T4 to S5 (Engquist et al., 1977), although this is ineffective in preventing insulin suppression (Brandt et al., 1976a). It is likely that extradural analgesia merely postpones the hyperglycaemic and adrenocortical responses until the period after operation (Lush et al., 1972; Engquist et al., 1980). The desirability of such an extensive blockade for pelvic surgery has been questioned by Cooper and colleagues (1979).

Bromage, Shibata and Willoughby (1971) examined the effect of extradural analgesia on blood glucose and plasma cortisol values during thoracic and upper abdominal surgery. In spite of adequate pain relief, with blockade up to C6 if necessary, there was no reduction in the cortisol response although the hyperglycaemia was virtually abolished. Bromage and colleagues suggested that the inability to inhibit the adrenocortical changes was a result of the stimulation of vagal afferent fibres during surgery. If this interpretation is correct, then local analgesic techniques will only be of value in abolishing the hormonal response to pelvic and limb surgery.

High-dose opiate anaesthesia. While extradural analgesia has many benefits apart from its effect on the metabolic response, and is a clinically acceptable procedure, high-dose opiate regimens are suitable only for carefully selected and supervised patients because of the problems of respiratory depression after surgery.

Morphine 4 mg kg^{-1} (George et al., 1974; Brandt et al, 1978) and fentanyl 75 µg kg^{-1} (Stanley, Philbin and Coggins, 1979) have been shown to inhibit the hormonal and metabolic response to cardiac surgery until the start of cardiopulmonary bypass. Profound endocrine changes occur at this time which are not influenced by the opiate and are probably caused by factors such as hypothermia, non-pulsatile flow and the sudden increase in blood volume with haemodilution. Hall and others (1978) observed that fentanyl 50 µg kg^{-1} prevented the increases in blood glucose, plasma cortisol and plasma growth hormone concentrations found during prolonged pelvic surgery, but the study was not extended into the period after operation.

These attempts to inhibit the endocrine response to surgery, either by local analgesic techniques or by high-dose opiate anaesthesia, demonstrate further the complexity of the interrelationships between hormonal activity and substrate mobilization. It is noteworthy that, in all studies in which the cortisol response to surgery was abolished, no ill-effects were observed in these patients. This suggests that vigorous steroid supplementation for patients on long-term steroid therapy is unnecessary.

Substrate administration. Recent developments in enteral and parenteral feeding techniques permit vigorous nutritional support, replacing or even exceeding the calorie and nitrogen requirements of the catabolic patient. An appropriate calorie and nitrogen intake can reduce protein loss and possibly improve the prospects of survival in severely catabolic patients. It is important to note that the infusion of some parenteral nutrition solutions stimulates hormone secretion and this may exacerbate the endocrine changes after surgery. For example, the administration of amino acid solutions produces an augmented glucagon secretion following major abdominal surgery (Foster et al., 1980).

Hormone supplementation

Insulin. The recognition of the occurrence in the surgical patient of insulin suppression followed by resistance prompted the use of insulin infusions to decrease catabolism. Hinton and colleagues (1971) reported that the combination of glucose, insulin and potassium was effective in reducing the excessive protein breakdown in patients with burns, but failed to distinguish between a specific action of insulin and the result of giving extra calories. Woolfson, Heatley and Allison (1979) recently resolved this conflict by demonstrating a protein-sparing effect of insulin in catabolic patients, although they were unable to shed any light on the precise mechanism of action of insulin.

Growth hormone. Wilmore and colleagues (1974) observed that the daily i.m. administration of 10 iu of growth hormone improved the nitrogen balance in patients with severe burns maintained on an adequate calorie and nitrogen intake. Growth hormone supplementation produced a marked increase in insulin secretion which was probably responsible for the beneficial effects observed.

Anabolic steroids. The administration of methanedione in the period after operation caused a reduction in nitrogen excretion not only after herniorraphy, but also following gastric surgery (Johnston and Chenneour, 1963).

Environmental temperature. Cuthbertson and colleagues (1972) reported a reduction in protein catabolism in patients with fractures of the major long bones of the lower limb maintained at an environmental temperature of 28–30 °C.

Unfortunately, Spivey and Johnston (1972) were unable to demonstrate any beneficial effects on nitrogen loss of nursing patients after abdominal surgery at 30 °C, possibly because of the less severe injury. It is likely that the main application of this technique will be in the management of burns patients (Wilmore et al., 1976), although the precise mechanism by which the protein catabolism is ameloriated has not been elucidated.

Influence of anaesthesia. The endocrine response to anaesthetic agents *per se* has been comprehensively reviewed (Oyama, 1973). With the exception of diethyl ether, the influence of modern inhalation and i.v. agents on hormone secretion and metabolism is small compared with that of surgical stimulation provided that hypoxaemia, acidosis and hypothermia are avoided. Indeed, halothane may even be beneficial as it has been shown to reduce adrenaline secretion *in vitro* and *in vivo* (Roizen et al., 1974; Halter, Pflug and Porte, 1977).

CONCLUSION

The neuroendocrine response to trauma appears to have evolved to assist survival in a more primitive environment by providing appropriate substrates to maintain the function of vital organs. However, in modern anaesthetic and surgical practice where severe physiological disturbances are prevented or rapidly treated, and suitable substrates made readily available, any benefits of this response are no longer apparent. The aim for the future must be the safe prevention of surgically-induced, adverse hormonal and metabolic changes. We consider that it is no longer necessary to defend the charge of attempting to reduce such changes by various anaesthetic techniques, but rather to ask why these effects should be left unaltered.

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THE SCIENTIFIC BASIS OF NUTRITIONAL ASSESSMENT

A. W. Goode

Nutritional assessment is the essential first step in the adequate nutritional care of a patient. Simple bed-side impressions of nutritional status or change with therapy are invariably erroneous (Walesby et al., 1979) and are to be deprecated. Recent surveys (Bollet and Owens, 1973; Bistrian et al., 1976; Hill et al., 1977; Letsou, Connaughton and O'Donnell, 1977; Willicutts, 1977) have shown that up to 50% of patients in hospital were moderately or severely malnourished. Malnutrition may have a profound influence upon clinical practice. Acute weight loss of more than 40% is invariably fatal while degrees of wasting are associated with increasing mortality and morbidity. Such depletion results in poor wound healing and callus formation, immunological depression, disordered coagulation, reduced enzyme synthesis, altered drug metabolism, decreased tolerance to radiotherapy and chemotherapy, and prolonged convalescence after surgery.

The formulation of an appropriate feeding regimen for the wasted patient can only be done after accurately establishing the nature and degree of depletion. However, a recent study (Ray and Dickerson, 1979) has shown that clinicians faced with many available tests are both uncertain about those most appropriate, and confused as to the ultimate aim of management.

Brozek and Henschel (1961) described how Rubner in 1902 conceived the idea of an oxidizing protoplasmic mass as the component of the body responsible for energy consumption and chemical and mechanical work performed. Moulton (1923) reinforced this concept, showing that body fat was a variable quantity and emphasized the constant composition of the lean body weight; which on analysis was hydrated and both nitrogen- and potassium-rich in contrast to neutral fat. Since then Kinney, Lister and Moore (1963) have demonstrated that resting energy expenditure was directly related to the size of the lean body mass. Thus body weight is composed of the relatively inert skeletal mass, body fat—the portable personal energy store,—and the energy-utilizing component, the lean body mass. Moore and colleagues (1963) further refined the concept of the lean body mass, pointing out that some of its constituent tissues—dermis and connective tissue—are functionally inert; thus they proposed a more precise term for the active cellular mass: the body cell mass.

Peaston (1974) studied weight loss in long-term starvation and concluded that the body utilizes fat and the skeletal muscle component of the body cell mass in a ratio of 2.5 : 1. Similarly, Burkinshaw, Morgan and Hill (1978), studying weight loss before operation, concluded that protein was lost from skeletal muscle, but that in the patient after operation two-thirds was lost from skeletal muscle and the remainder from visceral protein. Regardless of the source of the protein utilized to provide glucose by gluconeogenesis, the loss of body cell mass represents the increasing inability of the body to utilize energy to support vital functions and ultimately will lead to death. Accelerated loss—hypercatabolism—is seen in burns, sepsis and acute pancreatitis. Thus, from theoretical considerations, measurement of total body protein (the body cell mass) is the most important single parameter.

General indices of nutritional depletion

In clinical practice the critical factor initiating nutritional assessment is awareness of the possibility that the patient may be wasted. A routine clinical history usually neglects nutritional intake and a specific dietary history may be most valuable in revealing specific deficiencies (Mueller and Thomas, 1975). Weighing the patient is the simplest guide to nutritional deficiency although it gives no indication of the nature of the tissue loss and may be misleading in clinical conditions with water retention or dehydration. The comparison of actual weight with ideal weight for height and age derived from anthropometric tables (Documenta Geigy, 1962; Kemsley, Billewicz and

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Thompson, 1962; Jelliffe, 1966) gives a guide to the severity of depletion. The calculation of percentage weight loss and its interpretation with time is shown in table I (Blackburn et al., 1977).

TABLE I. *Evaluation of percentage weight loss. Weight loss calculated using the equation: percentage weight change = (usual weight − actual weight)/(usual weight) × 100*

Time	Significant weight loss (%)	Severe weight loss (%)
1 week	1–2	> 2
1 month	5	> 5
3 months	7.5	> 7.5
6 months	10	> 10

Another simple measurement is the mid upper-arm circumference of the non-dominant arm. Reduction to 85% or less of adult standard values is associated with significant morbidity after surgery (Kammerling, Foster and Karran, 1978). Standard adult values and their interpretation are given in table II.

TABLE II. *Arm circumference values in adults. The measurement should be made in the middle of the non-dominant arm*

	Male (cm)	Female (cm)
Standard	29.3	28.5
90% of standard	26.3	25.7
80% of standard	23.4	22.8
70% of standard	20.5	20.0
60% of standard	17.6	17.1

Fat stores

Measurements of body fat are an estimate of endogenous energy stores, some measuring the absolute size and others dynamic function. Triceps skinfold thickness measured on the non-dominant arm with skinfold calipers will give a simple measure of suspected loss of body fat. Standard values for adults and their interpretation are given in table III. Measurement of skinfold thickness at four sites—mid-biceps, mid-triceps, subscapular and suprailiac—may be used to determine the absolute size of the body fat being expressed as a percentage of body weight (Durnin and Womersley, 1974).

TABLE III. *Triceps skinfold thickness values in adults*

	Male (mm)	Female (mm)
Standard	12.5	16.5
90% of standard	11.3	14.9
80% of standard	10 0	13.2
70% of standard	8.8	11.6
60% of standard	7.5	9.0

The rate of clearance of injected intralipid—an i.v. fat tolerance test—is a measure of fat utilization (Feggetter, 1980). The clearance of a bolus injection occurs at two rates, $K1$ and $K2$. $K2$ is a first-order reaction where clearance is exponential and a constant fraction is removed. The clearance curve is plotted semilogarithmically and the regression line fitted by the least squares method. The slope of the regression line is the fractional clearance rate. Surgery and heparin therapy increase the exponential ($K2$) clearance.

In patients whose dietary intake is known to be inadequate, there is an increase in ketone body production which may reduce gluconeogenesis from protein (Wedge et al., 1976). Conversely, failure of ketone production may be of serious consequence as energy will then be principally derived from protein stores (Williamson et al., 1977). Rich and Whitehouse (1979), investigating ketone body production in the wasted patient before operation, have observed that, in patients similar in all other nutritional parameters, those who were unable to produce more ketone bodies after a 6-h fast had a significantly greater mortality rate after surgery.

Essential fatty acids have three principal functions: as energy substrates, in the synthesis of structural lipoprotein and as precursors for prostaglandin synthesis (Press, 1980). Diagnosis of deficiency states have in the past been dependent upon recognizing specific clinical features of deficiency—dermatitis, diarrhoea, abnormal platelet function and fatty infiltration of the liver. Patients fed on regimens composed only of amino acids and glucose and patients with extensive bowel resections are especially liable to develop essential fatty acid deficiency. The basic essential fatty acids which can only be synthesized by plants are linoleic and linolenic acids; as about 10% of adipose triglyceride is linoleic acid, there is a considerable reserve. The enzymes which convert linoleic acid to arachidonic acid are also capable of converting the non-essential oleic acid to eicosatrienoic acid. In normal circumstances linoleic acid is the preferred substrate. However, in fatty acid deficiency oleic acid inhibition is removed and eicosatrienoic acid concentrations become detectable. A ratio of eicosatrienoic acid/arachidonic acid of 1.0 or less is diagnostic of deficiency.

Protein stores

This is the most important nutritional component and the majority of available tests are directed towards measuring the total size of the body cell mass, reflecting the relative daily change of tissue synthesis or breakdown rate. Plasma amino acid profiles are altered by the underlying disease process in the wasted and fasted patient. In chronic protein calorie malnutrition total amino acids are decreased, particularly branched-chain amino acids, while glycine and serine are usually increased (Waterlow and Harper, 1975). In infections total amino acids concentrations are again decreased, with increase in phenylalanine and tryptophan (Wannemacher et al., 1972). After surgery there is a progressive decrease in the glucogenic amino acids for up to 3 days with a corresponding increase of branched-chain amino acids (Dale et al., 1977). In patients with cancer alanine, arginine and branched-chain amino acids values are decreased whilst, in contrast to starvation, glycine is normal or decreased (Glass and Goode, unpublished observations).

However, amino acid analysis facilities are limited and interpretation of individual patterns may be difficult as well as not quantifying tissue loss from the body cell mass.

Indices of total body protein

Absolute size of the body cell mass may most simply be quantified by measuring the fat-free mass using Durnin and Womersley's method (1974) of skinfold thickness measurements. This gives the percentage of body weight as fat and, by simple calculation, the fat-free mass in kilograms may be derived. In patients clinically free from oedema and with a normal packed cell volume this gives excellent agreement with other more complicated but precise methods of measurement (Goode and Hawkins, 1978).

The two methods which most precisely measure the body cell mass—total body nitrogen and total body potassium—are complex and not suitable for daily clinical practice except in specialized centres. They are, however, accurate research techniques and provide the basis for body composition analysis and a critical evaluation of other methods of determining nutritional status and nutritional support. Both measure elements abundant in the body cell mass, but not in neutral fat. Total body nitrogen is measured by neutron activation analysis (Oxby et al., 1978) and has been used in body composition analysis after surgery (Collins, Oxby and Hill, 1978). Similarly, the estimation of total body potassium by the measurement of potassium-40 in a whole body monitor is a good index of body cell mass in the non-acidotic patient not undergoing insulin therapy (Hawkins and Goode, 1976), and may also be used to monitor nutritional change (Goode et al., 1976). Administration of the isotopes potassium-42 or potassium-43 to measure body cell mass may produce an underestimate of up to 12%, as the isotope may not completely exchange with bone within the standard time (Goode and Hawkins, 1978).

In clinical practice the absolute size of the muscle mass is most easily measured by two methods: mid-arm muscle circumference can be calculated from the mid-arm circumference and the triceps skinfold thickness from the formula: Mid-arm muscle circumference = mid-arm circumference $-(\pi \times$ triceps skinfold thickness$)$. The value obtained can then be compared with standard values (Jelliffe, 1966).

In skeletal muscle creatine is irreversibly converted to creatinine at a reasonably constant rate. Measurement of urinary creatinine will thus give an estimate of the total skeletal mass. For accuracy three consecutive 24-h urinary collections should be performed. The values obtained are compared with those from well-nourished subjects of the same height as shown in standard tables (Blackburn et al., 1977). Values of only 60–80% of normal are indicative of moderate malnutrition, while values less than 60% indicate severe depletion. Future studies assessing muscle function may involve relating size to simple tests of optimum muscle strength such as hand grip strength.

Indices of relative protein change

Nitrogen balance is one of the most widely used methods of assessment. The daily comparison of a known intake with nitrogen loss from all sources allows a measure of the relative change of the body cell mass. It does not estimate the absolute size of the body cell mass. A positive nitrogen balance, where intake and retention exceeds loss, is indicative of anabolism; excess loss indicates tissue catabolism. It has been suggested that compounding errors in collection may decrease its value after about 14 days. A negative nitrogen balance of 1 g indicates a loss of 6.25 g of protein or 30 g of muscle tissue.

Tissue synthesis rate may be most accurately measured by estimating whole body protein turnover by a constant rate infusion of ^{14}C-leucine or ^{15}N-glycine (O'Keefe, Sender and James, 1974). From this the anabolic rate may be calculated, while Clague and others (1980) have used ^{14}C-leucine incorporation into plasma proteins as an index of the severity of injury. More simply, hair root morphology has been advocated as an indicator of protein synthesis with feeding (Jourdan, 1978).

Muscle breakdown is determined by measuring excretion of 3-methylhistidine, which is released from actin and myosin in skeletal muscle. 3-Methylhistidine when released is not reutilized, and is excreted unchanged in the urine (Young et al., 1972). Provided that a meat-free diet is taken for 24–48 h before measurement, 24-h urinary estimations may be made. The rate of muscle catabolism may be quantitated as 4.2 µmol of 3-methylhistidine represents 1 g of mixed muscle protein (Munro, 1978).

Visceral protein status

Serum albumin concentrations have most commonly been used as an index of hepatic protein synthesis. The plasma concentration is dependent not only upon the synthetic rate, but also the catabolic rate and distribution between the intra- and extra-vascular compartments (Fleck, 1976). Serum concentrations from 30 g litre^{-1} to 21 g litre^{-1} are indicative of moderate malnutrition, while values less than 21 g litre^{-1} indicate severe malnutrition. No relationship has been demonstrated between low values and nutritional oedema (Golden, Golden and Jackson, 1980). In stable patients albumin concentrations have been used both as a nutritional index of longstanding malnutrition and to monitor the response to nutritional support (Olusi et al., 1975). Serum albumin concentrations show a poor response to short-term changes in protein and energy intake; on a daily protein intake of 20 g only a small decrease in serum albumin can be induced in 5 weeks.

Proteins synthesized by the liver but with a short half-life have been used as indices of visceral protein synthesis and are more responsive to refeeding. Serum transferrin is reduced in protein calorie malnutrition and has a half-life of 8 days (Awai and Brown, 1963). Serum transferrin may be measured directly using commercially available kits or indirectly from total iron binding capacity from the formula: Serum transferrin (mg dl^{-1} = (Total iron binding capacity × 0.8) − 43. The normal values are 200–300 mg dl^{-1}. Serum concentrations between 100 and 150 mg dl^{-1} are indicative of moderate malnutrition and values less than 100 mg dl^{-1} reflect severe malnutrition. Caution must be used in patients with a history of chronic bleeding as increased concentrations of transferrin may occur. Plasma thyroxine-binding pre-albumin has a half-life of 2 days and may be used as a short-term nutritional index (Ingenbleek et al., 1975). Retinol-binding protein is, however, the most sensitive index of both subclinical malnutrition and the response to feeding, with a half-life of 12 h (Shetty et al., 1979).

Immune status

Adequate nutrition is essential for the maintenance of a normal immune system (Law, Dudrick and Abdou, 1974). A reduction in the total peripheral lymphocyte count is associated with depressed cellular immunity. A total lymphocyte count of 800–1200 mm^{-3} is indicative of moderate protein calorie malnutrition and less than 800 mm^{-3} indicates severe depletion. Circulating immunoglobulins may be directly measured as a standard laboratory procedure. Immunological challenge tests are also often used as a test of the cell-mediated immune response. Intradermal injection of a common recall antigen—candida, PPD, streptokinase, streptodornase or DNCB—should produce a cutaneous response within 24–48 h. A skin weal 0.5 cm or more in diameter is a positive response. Failure to respond indicates an anergic state, but the test may become positive with appropriate nutritional support.

Vitamin status

Daily requirements of vitamins vary greatly, for example the dose of vitamin C is 50 000 times that for vitamin B12. A good nutritional history is essential as often it will indicate a deficiency before its clinical manifestations. The requirements for the water-soluble vitamins are especially increased in disease states (Levenson et al., 1976). Vitamin C depletion is found in smokers, in associtiion with aspirin and barbiturate therapy, and in postoperative patients. Decreased vitamin B6 concentrations are found with oral contraceptives and isoniazid therapy, vitamin B12 deficiency with oral hypoglycaemic agents, and low folate values with epileptic therapy, methotrexate treatment and excess alcohol intake. A combination of low vitamin A, B6 and C values is known to depress the immune response. Vitamin K deficiency may occur with broad-spectrum antibiotic therapy.

There are two types of test for vitamin status: blood concentrations or the measurement of an enzyme activity in which a vitamin is a co-factor (Sauberlich, Doway and Skala, 1974). Plasma vitamin A, C, B12 and folate concentrations reflect recent dietary intake, while leucocyte ascorbic acid and red cell folate values are indices of whole body status. Vitamin B1 (thiamine) status is measured by red cell transketolase activity and vitamin B6 (pyridoxine) status by red cell aspartate transaminase activity. Four coagulation factors are vitamin K-dependent, but deficiency is usually measured by a prolonged cephalin–kaolin time and a prolonged prothrombin time.

Trace element status

The body contains approximately 40 elements present in varying amounts; those present in adults in the concentration of about 100 parts per million are the trace elements. Up to 15 trace elements are essential for optimal health (Aggett, 1979). Some trace metals form complexes with organic molecules and are involved in cell membrane function while others are involved with enzyme function. Indeed, about one-third of all enzymes are trace metal dependent. Copper is involved with cellular respiration, zinc in carbonic anhydrase function, nucleic acid and protein synthesis and the urea cycle, selenium in peroxide reduction, manganese in glycoprotein synthesis and molybdenum in sulphur metabolism.

Trace metal deficiencies are usually associated with gross malnutrition or prolonged nutritional support, especially parenteral nutrition, and circulating zinc, copper, magnesium and chromium concentrations must be measured. In some instances various clinical manifestations may give a suspicion of deficiency. Zinc depletion is associated with anaemia, dermatitis, diarrhoea, and impaired wound healing, copper with iron-resistant anaemia and osteoporosis, and chromium with glucose intolerance and peripheral neuropathy.

Awareness that a patient may be nutritionally depleted is the key to assessment and management. A dietary history and clinical examination are of great value in indicating possible specific deficiencies. However, specific tests are of most value. No single abnormal parameter should be used in isolation to identify malnutrition, but rather a combination of at least three parameters. Those selected by the clinician obviously depend upon his understanding of their limitations and laboratory availability. In general, anthropometric measurements will indicate moderate or severe degrees of malnutrition and during a feeding regimen will show evidence of successful repletion if performed at approximately 2-week intervals (Goode et al., 1976; Shenkin and Steele, 1978).

Collins, McCarthy and Hill (1979) studied degrees of weight loss, arm circumference and arm muscle circumference with total body nitrogen content. They concluded that anthropometry was reliable, the 95% confidence limits were nitrogen ± 30 g, but the variance shown made it inappropriate as a single measurement. Similarly, anthropometry was not reliable in following changes in body protein in individual patients over a short period of time.

A frequently recommended triad for nutritional assessment has been a recent weight loss in excess of 10%, serum albumin less than 32 g litre^{-1} and loss of skin antigen recall. Mullen and others (1979) studied 16 nutritional parameters and concluded that only serum albumin and serum transferrin concentrations with delayed hypersensitivity reactions had a significant predictive value of morbidity and mortality after operation; patients with these reduced parameters had a 2.5-fold increase in complications, although the prognostic accuracy of delayed hypersensitivity has been disputed (Brown et al., 1980).

During nutritional support, either enteral or parenteral, it is essential to measure changes in nutritional status, circulating substrates and ions, and organ function at prescribed intervals.

Programmes for daily, twice-weekly and weekly measurements of these parameters are given in tables IV–VI.

Advances in the understanding of the consequences of malnutrition and its management by

TABLE IV. *Daily monitoring during a feeding regimen*

(1) Body weight
(2) Fluid balance
(3) Haemoglobin, p.c.v. and white cell count
(4) Blood urea and electrolytes
(5) Blood glucose
(6) Acid–base status
(7) Urine and plasma osmolality
(8) Nitrogen and electrolyte content of urine, gastrointestinal and fistula loss
Additionally during enteral feeding:
(9) Stool frequency, volume and consistency

TABLE V. *Twice weekly monitoring during a feeding regimen*

(1) Serum calcium
(2) Serum phosphate
(3) Serum magnesium
(4) Serum proteins
(5) Liver function tests
(6) Clotting studies

TABLE VI. *Weekly monitoring during a feeding regimen*

(1) Serum B12 and folate
(2) Serum lactate
(3) Serum iron
(4) Serum triglycerides
(5) Trace elements

appropriate nutritional support have been a major advance in patient care. It is surprising, therefore, that therapy has often not been preceded by measurement to allow the most appropriate regimen to be provided. The selection of the appropriate tests for assessment of nutritional status before and during management can be critical for a successful outcome. The formation of nutritional care teams is an additional source of expertise now available, which can be of particular value in the management of the complicated patient.

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PRINCIPLES OF ENTERAL AND PARENTERAL NUTRITION

J. POWELL-TUCK AND A. W. GOODE

Weight loss is universally recognized as a complication of severe illness, and it has been a medical and nursing axiom for centuries that patients should be encouraged to eat in order to maintain or regain their strength. Techniques of enteral and parenteral feeding now enable us to feed patients who might otherwise be unable to eat or assimilate enough normal food. Parenteral feeding is capable of restoring the weight and body cell mass of a chronically sick patient and maintaining them at normal values over years if necessary.

Interest in nutritional therapy for the anaesthetist or for the member of an intensive care team will be two-fold:

(1) How does the nutritional state of a patient before operation influence his chance of complication-free surgery and therefore when should preoperative restorative feeding be encouraged or insisted upon?

(2) How can nutritional support be used to benefit the acutely ill patient following trauma, or during critical illness?

Using such treatment we aim to maintain organ function, promote healing, strengthen the patient and thereby reduce morbidity and hasten mobilization and convalescence. Nutritional treatment can enhance immunological responses, particularly of cell-mediated type, and therefore may improve endogenous defences against infection. Our order of priority for enteral or parenteral fluid therapy will be:

(1) to maintain the circulation;

(2) to achieve water and electrolyte replacement and balance;

(3) to prevent and replace loss of body cell mass.

Nutritional treatment inevitably modifies or enhances the metabolic responses to an illness such as energy consumption, protein turnover and hormonal output, and much research is aimed at delineating and understanding these changes. However, at present we know little of how the changes influence the outcome of the disease. They therefore remain the province of the research worker. We shall return to some developments towards the end of this paper.

REQUIREMENTS

Dietary standards and recommendations for oral, enteral and parenteral feeds are given and discussed elsewhere (Davidson et al., 1979). Table I shows the inputs of individual nutrients we use with success for parenteral feeding.

TABLE I. *Ranges of commonly used daily nutrient intakes for parenteral nutrition. Energy is supplied as glucose and Intralipid. Linoleic acid, an essential fatty acid, is a major constituent of Intralipid. The normal range we give is 90 g per week to 45 g per day, that is 1000 ml per week to 500 ml per day, of 20%. At present we do not give vitamins D and Biotin routinely *Supplied as Multibionta 4 ampoules weekly*

Nitrogen 8–20 g
Energy 1500–4000 kcal
Electrolytes and trace elements
  Sodium 70–220 mmol
  Potassium 60–120 mmol
  Chloride 70–220 mmol
  Calcium 5–10 mmol
  Magnesium 5–20 mmol
  Phosphate 20–40 mmol
  Zinc 2–7 mg
  Copper 1.6 mg
  Selenium 120 µg
  Iodine 120 µg
  Chromium (trivalent) 5–0 µg

Vitamins
  A* 5700 iu
  B1* 28.6 mg
  B2* 5.7 mg
  Nicotinamide* 57 mg
  Pantothenate* 14.3 mg
  B6* 8.6 mg
  C* 286 mg
  E* 2.9 mg
  Folic acid 15 mg per week
  K1 10 mg per month
  B12 250 µg per 2 months

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Energy (Munro, 1951; Kinney et al., 1970; Stoner, 1970; Wilmore, 1977)

Energy, supplied as fat or carbohydrate (or protein), is required to provide for the patient's metabolic rate plus his suprabasal requirements resulting from activity, nutrient intake (specific dynamic action), the environmental temperature, disease and trauma. Resting metabolism can be measured clinically by indirect calorimetry or assessed by use of nomograms using height and weight. Alternatively Kleibers formula (see Wilmore, 1977) of metabolic rate (kcal day^{-1}) = 70 × (body weight (kg)$^{3/4}$ is useful now that pocket calculators readily determine values to the power of $\frac{3}{4}$. If a normal subject is placed in surroundings of temperature less than a "critical temperature" of about 25 °C his heat production (thermogenesis) increases either associated with or without shivering. This critical temperature decreases after injury. Kinney and co-workers (1970) studied the resting metabolic expenditure of patients after operations of varying severity. Most procedures do not result in an increased energy expenditure of more than 10%. However, certain conditions such as multiple fractures, severe sepsis or peritonitis and particularly large area burns can increase resting expenditure by 30–100% or more. For most adults (and this includes many of those requiring intensive care) energy requirements will be exceeded and fat accumulation will occur on 40–50 kcal kg^{-1} day^{-1}. In the very malnourished patient this is perhaps better expressed per kg ideal body weight. In adolescents in whom growth is required inputs should be 60 kcal kg^{-1} day^{-1} or more, and in young children should be much higher (Waterlow, Golden and Patrick, 1978).

It is still uncertain as to whether a fat calorie is equivalent to a carbohydrate calorie in human nutrition; it seems as if there is approximate equivalence but as a general rule it is probably wise to provide a minimum 500 kcal day^{-1} as carbohydrate to cover cerebral requirements even though it is now known that the brain is capable of adapting to ketone metabolism.

Protein (nitrogen) (Munro, 1951, 1972; Cuthbertson and Tilstone, 1969)

Nitrogen metabolism is most commonly assessed by a balance technique. in the healthy fully grown adult taking a normal diet there is nitrogen equilibrium so that the intake of nitrogen equals the output. The intake is the dietary nitrogen while the clinically important outputs are urinary and faecal. Table II shows typical normal nitrogen losses in their various forms. It can be seen that urinary urea, which is the end-product of most amino acids oxidized, is the largest contributor, and it is usually only in severe protein-losing enteropathy like active inflammatory bowel disease, that allowances of more than nitrogen 1 g day^{-1} have to be made to cover faecal loss. In the well-nourished man in nitrogen equilibrium, increase in intake above his usual diet will be balanced by increased oxidation, and nitrogen balance maintained. It is only the adult with protein depletion who needs excess nitrogen to maintain a positive balance while he rebuilds his lean body mass.

TABLE II. *Typical 24-h nitrogen losses (g) in normal 65-kg man receiving protein 87.5 g (from Harper, 1975 and Munro, 1972)*

	Loss (g)
Urine	
Urea	11
Ammonia	0.4
Creatinine	0.6
Uric acid	0.2
Undetermined	0.6
Total	12.8
Other	
Faeces	0.8
Skin	0.2
Other	0.15
Total	1.15

Urinary nitrogen losses increase after injury (particularly in the young and well nourished). If illness is severe or prolonged such losses may result in nutritional depletion. Thus if we wish to prevent or treat prolonged negative balance in the injured or severely ill patient we shall need to give increased amounts of protein or amino acids. In the depleted patient we shall aim to achieve some restoration of lean body mass, while in the well-nourished patient our aim will be to maintain nitrogen equilibrium. The Appendix shows how nitrogen balance can be estimated simply.

Not only does nitrogen have to be supplied in the correct amount, but also in the correct form and with other nutrients. The human diet must contain sufficient amounts of the essential amino acids, isoleucine, leucine, valine, methionine, phenylalanine, tryptophan, lysine and threonine. These amino acids (which are in the L form) can either be given alone as the nitrogen source or in combination with "non-essential" L-amino acids. The optional non-essential amino acid content of a diet is not known, but egg protein is taken as a reference in which 51% of the amino acids are essential. The minimum daily requirement for egg protein if adequate non-protein calories and other nutrients are supplied is about 0.42 g/kg body weight in normal subjects.

Interrelationship between intakes of energy, protein and other nutrients (Rudman et al., 1975; Wilmore, 1977).

Nitrogen balance studies illustrate the importance of considering nutrients, not in isolation but in relationship to one another. As energy intake increases in a diet containing a fixed nitrogen content, nitrogen balance improves until it reaches a maximum plateau for that intake in that individual. This is the basis for the commonly recommended nitrogen : calorie ratios ranging from 1 : 200 to 1 : 400. These are useful practical guides, but have little scientific precision. The importance of other constituents of a diet like sodium, potassium, phosphate and zinc on nitrogen balance is becoming increasingly recognized, and it is likely that many others should be included in this list. The practical implication is that, for optimally effective nutritional treatment, many different food constituents must be supplied in adequate amounts; we should remember this particularly when using i.v. feeding.

ORAL, ENTERAL AND PARENTERAL FEEDING— CLINICAL PRACTICE

Food in whatever form should be reintroduced to the undernourished or the critically ill patient slowly and with care. In particular, the implications of refeeding upon sodium and water retention should be stressed (Gozansky and Herman, 1971). In Jamaica (Waterlow, Golden and Patrick, 1978) studies have been made of the relationship between variations in sodium pump activity and the acute fluid retention sometimes seen during the refeeding of infants with protein-energy malnutrition. It may prove to be important to ensure that vitamin, electrolyte and trace element status is corrected before attempting to achieve a rapid weight gain in severely malnourished individuals. Once an individual patient is thought to need special feeding and the nutrients required have been decided upon, then the feed should be provided in the simplest, cheapest way which is most pleasant.

Oral feeding (Davidson et al., 1979)

Ordinary food must be the first choice if the patient has a reasonable appetite, can swallow, and his gastrointestinal tract is usable. The close co-operation of the dietician is necessary and her knowledge of dietary assessment techniques and her ability to provide a known intake in acceptable form should be exploited to the full. Nutritional balance data can be achieved with sufficient accuracy for clinical purposes if good records are kept and particularly if weighed diets can be provided, or if duplicate feeds are kept and analysed. Supplementation can be achieved using palatable commercially available feeds, examples of which are shown in table III.

Enteral feeding (Johnston and Lee, 1978)

Technique. Enteral feeding can be achieved using a transnasal tube or via an enterostomy. For nasogastric or nasoduodenal feeding we favour the Vygon 6-gauge silicone rubber paediatric tube because it does not stiffen with time. When placement is difficult the tube can be chilled in a refrigerator to stiffen it a little, or the Clinifeed tube, which is supplied with a stiffener, can be used. Both tubes have internal diameters of about 1 mm.

Feeds should be infused rather than given as a bolus. A 1500-ml plastic container attached to a giving set of suitable length is convenient. Flow can be maintained either by gravity (controlled by roller or gate clamps or by one of the newer inexpensive devices now available) or by pump. Simple low-cost peristaltic pumps such as the Viomedex or Clinifeed models are suitable. The Viomedex pump is conveniently used with a specially designed bag and giving set with a silicone rubber insert. Each patient has two bags which are used alternately; while one is in use the other is washed, cleaned with dilute sodium hypochlorite and allowed to dry.

Choice of feed. Except under special circumstances (see the end of this article), whole protein-, fat- and glucose polymer-containing feeds are used

TABLE III. *Major constituents of some enteral feeds available in the U.K.* **Low lactose;* †*Contains MCT;* ‡*Should be added to milk;* §*kJ = kcal × 4.2*

Supplier	Name	Quantity	Energy (kcal§)	Protein (g)	Fat (g)	Na (mmol)	K (mmol)	Ca (mmol)	Mg (mmol)	P (mmol)
	Cow's milk	1000 ml	650	33	38	22	38	30	5	31
Carnation Ltd	‡ Build up	1 pkt	132	25.6	0.2	5.4	9.8	8.3	0.9	7.9
Glaxo Ltd	Complan	100 g	444	20	16	15.2	21.8	18.3	2.9	18.7
Scientific Hospital Supplies Ltd	Albumaid*	100 g	305	76	—	54	3.8	7.5	8.5	10.7
	Maxipro*	100 g	352	88	—	10	11.5	7.5		12.5
	Metabolic Mineral mix*	100 g	—	—	—	172	212	205	40	192
BDH Pharmaceutical Ltd	Triosorbon*†	85 g (1 pkt)	400	16.2	16.2	17	17	5.1	3	7.7
Roussel Laboratories Ltd	Clinifeed 400 Vanilla	375 ml (1 tin)	400	15	13.4	10.5	12.4	5	2	7.4
	Clinifeed 400 Chocolate	375 ml (1 tin)	400	15	13.4	10.5	21	5	5.7	9.4
	Clinifeed 500 Vanilla	375 ml (1 tin)	500	30	11.0	12.8	21.6	3.3	1.9	9.0
	Clinifeed LLS*	375 ml (1 tin)	500	22.5	15.0	7.0	12.9	3.4	0.9	6.5
Abbot Laboratories Ltd	Ensure*	235 ml (1 tin)	241	8.7	8.7	7.6	7.7	3.1	2.0	1.6
Mead Johnson Laboratories	Portagen*†	100 g	464	16.5	22.5	9.6	15	11	3.9	10.7
	Isocal*†	355 ml (1 tin)	375	12.1	15.7	8.1	12	5.6	3.1	6.1
	Flexical*†	100 g	441	9.9	15	6.7	14.1	6.6	3.7	7.1
Eaton Laboratories Ltd	Vivonex Standard*	80 g (1 pkt)	300	6.3	4	11.2	9	3.3	2.4	1.4
	Vivonex HN*	80 g (1 pkt)	300	12.5	0.3	10.1	5.4	2.0	1.4	0.8

because they are cheaper and more physiological than elemental diets. Requirements have already been discussed. Table III shows some of the products available with their principal constituents.

Record charts. We need to know how much of each key nutrient a patient has *received* each day; for practical reasons this will sometimes be different from that prescribed. Accurate records of intake must be kept by the nursing staff, and the clinician or dietician should, by a knowledge of the contents of the prescribed feed, be able to translate the fluid intake into intake of any specific nutrient in which he is interested.

Recording of the outputs of urine, faeces and fistulae is also important if fluid balance is to be assessed. Balance studies of nitrogen, electrolytes or other nutrients will depend upon accurately timed collections of excreta, and biochemical assays. Body weight should be measured at least weekly, and urine sugar daily. A summary chart can be designed which includes spaces for daily intakes of principal nutrients such as energy, protein, electrolytes, vitamins and trace elements and outputs of fluid, sodium, potassium and urea or nitrogen, urine sugar and body weight. It is helpful also to leave room for plasma concentrations of electrolytes, urea and proteins, but these should be regarded as crude checks; day to day alteration of intake should rely most on balance data. Except in critically ill patients it is often possible to reduce blood sampling to once weekly after feeding is established.

Preparation of feeds. Feeds can either be prepared on the ward or in a central diet kitchen. The latter has advantages: if additives need to be made to proprietary preparations, stores can be kept centrally, proper weighing scales and electric blenders can be provided without duplication and mixing "tricks" and expertise are developed. When supplementary or elemental diets are provided for oral consumption, they can be presented and flavoured skilfully; for example, Vivonex can be presented as a fruit jelly. Finally, hygiene is readily encouraged, maintained and checked.

Complications. The various approaches described aim to limit the complications of enteral feeding. The soft, fine-bore tube helps prevent nasal and throat discomfort, and oesophageal damage in the longer term. The silicone rubber tubes can be left *in situ* for many weeks if necessary.

Sensations of gastrointestinal fullness are minimized by steady infusion (by pump if necessary) with gradual incrementation of intake over a week or so. Diarrhoea and vomiting are also minimized in this way. Very hypertonic feeds are best avoided usually and it may be necessary to avoid lactose in intolerant patients. High fat intakes are better avoided in patients with severe steatorrhoea, to reduce fluid and electrolyte losses. Medium-chain fatty acid-containing triglycerides can be tried in steatorrhoea, because such fatty acids are less dependent for absorption on bile salts and pancreatic lipase, but in some cases exacerbate diarrhoea. Contamination of the feed can also cause diarrhoea and the risk is minimized by good hygiene, and refrigeration of the feed between mixing and use. Feeds not used within 1 day are probably best discarded.

Metabolic complications and deficiency syndromes are prevented by careful feed design and prescription, with accurate record-keeping, screening and charting. Care is needed to ensure that patients do not become hyperglycaemic; insulin is prescribed as required. The causes of the abnormalities of plasma bilirubin, transaminases and alkaline phosphatase which are sometimes associated with both enteral and parenteral feeding are not fully understood. Ill patients often have other unrelated causes of hepatic dysfunction. Fatty liver is commonly associated with malnutrition. Biliary stasis may occur in patients fed parenterally who are not taking food, and especially fat, by mouth. Sometimes none of these factors seems to be the cause, and histological examination reveals only mild portal infiltration. The problem is seldom so severe that feeding has to be stopped. Metabolic bone disease as a cause of increased alkaline phosphatase concentration should be borne in mind in undernourished patients.

Parenteral feeding (Johnston, 1977; Powell-Tuck, 1979; Karran and Alberti, 1980)

When adequate food cannot be instilled into or absorbed from the gastrointestinal tract, and the situation is not likely to be corrected early, then parenteral feeding may be indicated. Typical parenteral inputs are shown in table I. Table IV shows the composition of some solutions available in the U.K. If when we feed a patient parenterally our object is to achieve weight gain, that is gain in body cell mass and fat stores, then nutritional

TABLE IV. *Constituents of some solutions available in the U.K. for parenteral nutrition*

	Constituents of 1 litre	Energy (kcal)	N (g)	mmol of					
				Na	K	Mg	Ca	PO_4	HCO_3
Aminoplex 5	L Amino Acids (LAA) Sorbitol 100% Ethanol 5%	1000	5	35	15	—	—	—	—
Aminoplex 14	LAA	340	13.4	35	30	—	—	—	—
Vamin glucose	LAA 10% glucose	650	9.4	50	20	1.5	2.5	—	—
Vamin N	LAA	250	9.4	50	20	1.5	2.5	—	—
Aminosol 10%	Casein hydrol.	310	12–15	135	1.4	—	—	5	—
Travasol/ Synthamin 7S	LAA Sorbitol 15%	760	6.6	38	30	2.5	—	15	—
Synthamin 9	LAA	250	9.3	73	60	5	—	30	—
14	LAA	375	14.3	73	60	5	—	30	—
17	LAA	450	16.9	73	60	5	—	30	—
Aminofusin L600	LAA Sorbitol 10%	600	8.8	40	30	5	—	—	—
Electrolyte in dextrose A	20% Glucose	800	—	—	—	28	26	—	—
B	20% Glucose	800	—	—	60	—	—	60	—
Glucoplex 1000	24% Glucose	1000	—	50	30	2.5	—	18	—
1600	40% Glucose	1600	—	50	30	2.5	—	18	—
Glucose 20%		800	—	—	—	—	—	—	—
Intralipid 10%	Soya bean oil 10% Glycerol	1000	—	—	—	—	—	15	—
Intralipid 20%	Soya bean oil 20% Glycerol	2000	—	—	—	—	—	15	—

treatment will need to continue for weeks; apart from weight increments attributable to rehydration or overhydration, a gain of about 1 kg per week in the adult can be regarded as good progress. Parenteral nutrition will therefore commonly be a long-term treatment lasting weeks or months, unless the limitation of gastrointestinal function is short-lived, enabling later oral and enteral feeding. If our object in feeding the patient is to induce temporarily metabolic responses to nutrient intake such as increased whole-body protein turnover or energy expenditure, or if our object is to prevent weight loss during a short critical period of an illness, then feeding may realistically be considered for shorter periods of 1–2 weeks.

Techniques of i.v. feeding are designed to eliminate the main complications, which are: those related to means of vascular access; metabolic abnormalities, imbalances and deficiencies; sepsis.

Vascular access. Three main approaches to gaining access to the venous system have been tried for parenteral feeding: peripheral venous cannulation, central venous cannulation and arteriovenous shunts or fistulae.

Peripheral veins tend to thrombose rapidly after cannulation and this tendency is much increased by the infusion of hypertonic or acid solutions or of blood products. Thus low concentration amino acid and glucose solutions have to be used, and energy has to be supplied principally from fat emulsions such as Intralipid. Regimens supplying up to 80% of the energy as fat emulsions have been used successfully. Alternatively, isotonic amino acid solutions can be infused with electrolytes, vitamins and trace elements, but without a calorie source. Such an approach has been shown to be capable of improving nitrogen balance in short-term studies (Blackburn et al., 1973; Hoover et al., 1975; Greenberg et al., 1976), and may be worthy of consideration as an alternative to routine electrolyte and dextrose infusions after operation.

To supply more than 4–600 kcal as carbohydrate (100–150 g) without a large intake of water we will need to use some other means of vascular access. Attempts have been made to insert and use arteriovenous shunts or create a–v fistulae for long-term feeding, but experience discourages their use because they tend to thrombose in the non-uraemic patient. It is generally accepted that a central venous catheter is best.

A central venous catheter used for parenteral feeding has certain differences from one used for central venous pressure monitoring. The nutritious solutions infused through it can support the growth of bacteria and *Candida*. It will often need to remain in place for periods of weeks or months. Thrombosis of central veins is a major risk of parenteral nutrition and may not always be immediately clinically apparent. We favour the routine use of a silicone rubber catheter, inserted in operating theatre conditions using a full aseptic technique. The catheter should lie with its tip near the junction of the superior vena cava and right atrium, and should enter the subclavian vein on the flat anterior chest wall after passing just beneath the skin for 5–10 cm. A "skin-tunnelled" catheter such as this is readily inserted by a blind technique if the catheter has a detachable hub. We use an infraclavicular approach usually, but a supraclavicular technique can be used if preferred, provided care is taken when tunnelling the catheter over (or under) the clavicle on to the anterior chest wall, so that kinking cannot occur when the patient moves. A blind approach such as this carries a small (less than 5%) risk of pneumothorax. If this risk is not acceptable, a cut down to the cephalic vein in the deltopectoral groove can be used. The same catheter can be used, or alternatively the more sophisticated and expensive Broviac or Hickman catheters; these have a dacron cuff attached which is placed in the skin tunnel so that ingrowing fibrous tissue fixes the catheter after 2–4 weeks, thus obviating the need for fixing stitches. The advantages of such skin-tunnelled catheters are considerable. First, they are comfortable for the patient. Second, they are capable of use over periods of more than 1 year if care is taken to prevent sepsis and thrombosis; the catheter is soft enough not to cause intimal or more serious venous damage and is made of a material which is well tolerated and does not kink permanently. Third, the skin tunnel acts as an effective early warning system because organisms passing along the outside of the catheter from the skin surface must traverse the tunnel before reaching the blood stream and in so doing they cause visible inflammation. If a silicone rubber catheter is used, any inflammation visible at the skin puncture or along the skin tunnel is an indication for removing the catheter. Finally, because the catheter emerges at a site which is relatively flat even in the emaciated patient, it is easy for the nurses to dress. The entry site is cleaned with chlorhexidine in alcohol, sprayed with an iodophor powder, sealed with a plastic dressing spray such as "Opsite" and then covered with a simple semi-occlusive island dressing such as "Steripad". The process is repeated after bacteriological swabbing whenever the dressing becomes loose, or at least once weekly.

A simple arrangement for delivery of the nutrient fluids is desirable in order to enable busy nurses to make the necessary bottle, bag and giving set changes by a planned and organized aseptic technique. Tubing junctions which are potential sites for microbial invasion should be kept to the minimum; this is readily possible now that two- and three-limbed, single-piece giving sets are available. Giving sets should be discarded after each 24 h. The additions of vitamins, electrolytes and trace elements which will have to be made to the infusate must be done in ideal surroundings in a clean air unit with a laminar flow hood, by personnel observing full aseptic technique (gloves, sterile clothing, mask, etc.) and acquainted with the chemical compatibilities of the additives and the infusate. This role is properly played by the pharmacist. This approach can be taken a stage further so that the pharmacist mixes most or all of the nutrients required for a 24-h period into a single 3-litre capacity disposable Viaflex bag (Powell-Tuck et al., 1978). At present we cannot recommend the addition of fat emulsions into such mixtures because pharmaceutical testing raises doubt about their stability and therefore safety. Intralipid is infused separately. Such a bag greatly reduces the number of connections and bottle changes made by the nursing staff in the ward or intensive care unit. The method allows use of a single giving set, and is conveniently controlled, if desired, by a low-output pressure pump such as the Valleylab or Imed. The convalescent patient can be fed over periods of less than 24 h and the catheter spigotted and heparinized. If this is to be done the glucose containing infusion should be slowed for 30 min before stopping, to prevent rebound hypoglycaemia. Such temporary freedom from the catheter can considerably reduce the psychological dependence on the feed and on the nurse who changes it in patients fed in the long term. As convalescence progresses we now commonly teach our patients to make the 3-litre bag changes and catheter heparinizations themselves, further increasing their sense of independence. This is the basis of successful home parenteral feeding in patients with gastrointestinal failure.

The 3-litre bag approach need not present a problem in the acutely ill patient, where hour-to-hour flexibility is sometimes required. It is not usually desirable to make rapid changes in nitrogen or energy input, nor of essential vitamins or trace elements. Requirements of magnesium, calcium and phosphate are usually supplied in constant amount, but it is reasonable not to infuse calcium in the short-term and it can be omitted from the 3-litre bag if necessary. The main hour-to-hour flexibility required is in the supply of water, sodium, chloride, potassium and bicarbonate. These can all easily be supplied as commercially prepared solutions which can be given either centrally or peripherally. Additives by the nurses are not necessary; antibiotics and other drugs should be given by a separate peripheral infusion.

Once additives or mixtures have been made the container should be refrigerated until just before use. Solutions to which vitamins have been added are protected from the light not only during storage, but also during infusion. Care must be taken to see that vitamins not present in multivitamin preparations, particularly vitamin K, B12 and folic acid, and also vitamin D and perhaps others such as biotin, are supplied by other means (either orally, i.m. or i.v.).

Detailed records must be maintained. We need to know the actual amount infused (not prescribed) of the main nutrients including water, electrolytes, energy and nitrogen. We need to know whether adequate vitamins, essential fats and trace elements have been given. Output records of water, sodium, potassium and urea or nitrogen allow balances to be calculated and adjustments made. Finally, blood sampling allows crude week-to-week (more is often unnecessary) assessment of blood nutrient concentrations. As with enteral feeding, the emphasis is an adjustment by balance rather than by measurement of blood concentration.

INDICATIONS

There are at present no known absolute contraindications to supplying balanced nutrition to a patient, although there is some evidence that the course of malaria may be adversely affected by high protein feeds. The potential dangers of overenthusiastic early treatment of severe undernutrition have already been mentioned. A high energy intake gives rise to increased carbon dioxide production, particularly in the injured patient given glucose. This may have practical implications in the injured patient with respiratory failure when increases in carbon dioxide output of 56% have been documented (Askanazi et al., 1980). As a generalization, however, any patient who is weakened by food deprivation, or who will become so if left untreated, requires nutritional support. Ordinary food is the first choice if the patient can eat and assimilate it; liquid enteral feeds or supplements are used if the intake of food is the principal limiting factor; parenteral nutrition is reserved for those in whom it is impossible or impractical to provide adequate nutrition intestinally, or if for some reason it is undesirable to use the gut.

Table V shows the broad indications for enteral and parenteral feeding; however, none of the indications shown is absolute and decisions to instigate feeding or not depend upon how long the indication is likely to persist, the rate of weight loss and the patient's nutritional state.

Indications in special circumstances

Perioperative nutritional support. A number of reports have shown an association between poor nutrition before operation and morbidity and mortality after operation, whether the nutrition is assessed by weight loss, delayed hypersensitivity, plasma protein concentrations or whole body potassium measurement (Studley, 1936; Meakins et al., 1977; Harvey et al., 1978; Walesby et al., 1979). Support for the idea that the poor nutrition is the *cause* of the increased mortality and morbidity comes principally from animal studies. A high-protein diet allows wounds to heal quicker (Clark, 1919) and animals rendered hypoalbuminaemic by diet and plasmapheresis exhibit poor healing of abdominal wounds (Thompson, Ravdin and Frank, 1938) and after operation have weak colonic anastomoses which can be strengthened by nutritional treatment (Steiger et al., 1973). Controlled trials in humans have suggested also that parenteral feeding after operation can reduce surgical complications (Collins, Oxby and Hill, 1978) and feeding before operation can reduce mortality (Muller et al., 1980).

The use of peripheral infusions of isotonic amino acids to improve nitrogen balance after operation has already been mentioned. Intraduodenal feeding is also possible (Sagar, Harland and Shields, 1979). Nitrogen losses can be reduced in

TABLE V. *Indications for artificial feeding. *Short bowel or short circuits of the intestine (e.g. fistulae) can often be managed orally or enterally. Food has a trophic effect, enhancing intestinal adaptation to major resections of intestine. † These conditions are often associated with undernutrition resulting from reduced appetite, increased losses and sometimes intestinal short-circuiting. The undernutrition should be managed by means appropriate to its principal cause*

	Enteral	Parenteral
Reduced intake	+++	
Unconscious		
Diminished appetite		
Abnormal swallowing		
Partial oesophageal obstruction		
Increased demands	+++	(Supplementary)
Severe burns, trauma, infection/inflammation		
Intestinal failure causing undernutrition		+++
Abnormalities of motility (ileus, pseudo-obstruction, etc.)		
Chronic obstruction		
Short bowel or short circuit*		
Other causes severe malabsorption		
Intestinal diseases without undernutrition		?
Fistula†		
Inflammatory bowel disease†		
Special cases		
Renal failure	? Essential amino acids	
Hepatic failure	? Branched chain amino acids-enriched mixtures	

the catabolic patient by the use of insulin (Woolfson, Heatley and Allison, 1979) or anabolic steroids (Tweedle, Walton and Johnston, 1973), or by nursing the patient in a warm environment (Stoner, 1970). Similarly, it should be remembered that immobilization increases nitrogen losses. However, as yet we do not know whether negative balance *per se* is associated with poor healing.

Because it is probably neither justifiable nor practical on economic grounds to feed all patients undergoing surgery enterally or parenterally, it is tentatively recommended that patients who have lost 20% or more of their body weight should be treated nutritionally before operation if the operation can be delayed for 1–2 weeks, and should be supported after operation enterally or parenterally by the provision of a complete mixture of nutrients until adequate intake of normal food is possible. For critically ill patients following surgery, trauma or burns, especially if sepsis is present when weight loss can be greatly accelerated, much earlier feeding is indicated.

Enterocutaneous fistulae (Leading Article, 1979). The mortality rate from fistulae varies enormously according to site and aetiology. Comparison of results from different hospitals using varying treatments may be difficult. However, in hospitals where continued records have been kept there appears to have been a marked decrease in mortality over the past 20 years which may in part be explained by wider use of nutritional support by tube feeding, or by parenteral nutrition. There is no clear further reduction in mortality if nutritional support by parenteral nutrition is combined with stopping the patient eating and drinking. It is also not clear whether a period of "bowel rest" increases the spontaneous closure rate of fistulae, but it may often (but not always) reduce fistula drainage, thereby making skin care easier and the patient, though hungry, more comfortable. Bowel rest also seems to reduce the size of associated intra-abdominal abscesses and may therefore make later surgical treatment less difficult. It should be clear, however, that nutritional treatment is a supportive form of management, as are skin care and electrolyte replacement, and does not supplant the role of operative surgery.

Domiciliary parenteral nutrition (Jeejeebhoy et al., 1976). An increasing number of centres are developing expertise in maintaining and improving the nutrition of patients by the i.v. route in the very long term. Intermittent infusion is possible, allowing good rehabilitation in the home and return to work. Although such long-term treatment is usually not the province of the anaesthetist or the staff of an intensive care unit, it is important that such staff, who are deeply involved in the resuscitation of patients who may for example require massive small bowel resections, realize that such treatment is available in special centres, and that the degree of rehabilitation and quality of life can be very acceptable.

Bowel rest for inflammatory bowel disease. The idea that the inflammation of ulcerative colitis or Crohn's disease might tend to subside if the patient is prevented from taking food or drink enterally has been raised by many centres around the world. Food and drink certainly have many stimulatory effects upon the gut, including secretion of enzymes, fluid and electrolytes, bile and hormones, increase in motility and blood flow, and more rapid mucosal cell turnover. Food has a trophic effect upon the gut. No controlled evidence as yet supports the use of bowel rest as an anti-inflammatory treatment for colitis or Crohn's disease; the only trial showed no advantage for it in active ulcerative colitis. It seems wrong at present to advocate routine use of bowel rest even in acute diseases, bearing in mind the expense and potential dangers of parenteral feeding. However, when parenteral nutrition is indicated on nutritional grounds it may sometimes be worth a try to stop the patient eating. On present information we should not regard bowel rest as an alternative to proven drug therapy or surgical treatment.

INDICATIONS FOR SPECIAL FEEDS—GROWING POINTS

Patients in renal failure (Abel et al., 1973; Walser, 1977)

Patients in renal failure undergoing dialysis can and should be fed a normal or high-protein diet by the route appropriate to their particular needs. There has for a long time been interest in low protein (20–40 g) diets supplying all other nutrients in adequate amounts in the hope that the increased urea pool will be used as a source of non-essential nitrogen after conversion to ammonia following secretion into the gastrointestinal tract and bacterial metabolism. The efficiency of ammonia reutilization may depend upon the rate of intestinal clearance of urea from the blood, which appears to vary with diets of differing nitrogen content. The idea has been taken further and a chemically defined diet (given enterally or parenterally) containing essential amino acids as the only nitrogen source has been tried. A controlled study showed improved survival among patients with acute renal failure treated this way, compared with patients treated with glucose alone. Similarly, there is interest in the use of the carbon skeletons of the essential amino acids (their keto analogues) which can be aminated from the body's non-essential nitrogen and which can result in improved nitrogen balance. We need to know if such feeds used in conjunction with dialysis confer an advantage over normal feeds and dialysis.

Hepatic failure (Fischer, 1977; Adibi, 1980)

In hepatic failure from cirrhosis, plasma amino acids show a characteristic pattern with diminished concentrations of the branched chain amino acids and increased concentrations of various other essential and non-essential amino acids—particularly phenylalanine, methionine, tyrosine, aspartate and glutamate. Plasma amino acid concentrations in acute fulminant hepatitis also show low to normal branched chain amino acid values, while the concentrations of most others are increased. It has been suggested that high tyrosine concentrations in the blood and diminished competition from the branched chain amino acids for transport across the blood–brain barrier, result in high tyrosine brain concentrations. Tyrosine is normally hydroxylated to dihydroxyphenylalanine (DOPA) and noradrenaline but the enzyme which governs this has a K_m close to the normal tyrosine concentration. Thus as the concentration of tyrosine increases, so this amino acid is preferentially decarboxylated to octopamine, a false (ineffective) neurotransmitter. Noradrenaline synthesis is thought to be inhibited also by increased concentrations of tryptophan, phenylalanine and the false neurotransmitters octopamine and phenylethanolamine.

It has been suggested that infusion of a mixture rich in branched chain amino acids but deficient in tryptophan, methionine and phenylalanine might improve the state of the patient in hepatic coma or precoma, while allowing an adequate nutritional intake.

The infusion of branched chain amino acids or their ketoacids improves nitrogen balance in the normal or obese subject. An infusion of leucine results in a reduction in the concentrations of many other amino acids, probably as a result of enhanced muscle protein synthesis. Such increased synthesis has been demonstrated *in vitro*. Thus there is also growing interest in the use of branched chain amino acid solutions in catabolic patients not suffering from hepatic failure. At present, however, we do not know whether such infusions confer clinical benefit upon the patient, and trials are needed. Even if benefit is demonstrated, much work needs to be done to test the various hypothetical rationales for their use.

Elemental diet (Russell, 1975; Goode, 1977; Koretz and Meyer, 1980)

Elemental diets, in which food is presented predigested as amino acids or small peptides, short glucose chains with or without fat, and all the other nutrients required, have been advocated in a wide variety of illnesses. Such diets, represented in the United Kingdom by Vivonex and Flexical, are more expensive than diets containing whole proteins, and are probably no more efficient in the treatment of malnutrition. This may also be applicable even in patients with short bowels after extensive small intestinal resection. Elemental diets might be expected to have advantages in patients suffering from severe chronic pancreatic insufficiency although pancreatic extracts are readily available for addition to whole-protein feeds. It seems unlikely that elemental diets of fat, nitrogen and calorie content similar to, and administered by means comparable to those for whole protein liquid diets, result in different intestinal, pancreatic or biliary secretion. Their advantage may be in their ability to reduce greatly colonic faecal output, but again comparisons have not been made between elemental and non-elemental liquid feeds. They can prove useful in the patient with severe perineal disease for whom defaecation is painful. They have also been used as means of improving the nutrition of patients with multiple small intestinal strictures.

CONCLUSION

THE TEAM APPROACH

Successful enteral and parenteral nutrition depends upon good organization, record keeping and co-operation between many different people. *Nursing staff* bear much of the load and if they are to be expected to maintain accurate delivery of nutrients, correct records and, in the case of parenteral feeding, scrupulous asepsis, then care must be taken that they are not overloaded with work. A *specialist nursing sister* is invaluable if nursing programmes are to be developed, techniques taught and supervision maintained. Enteral feeds are best made up in a *central diet kitchen* under the supervision or guidance of the *dietician*. Thus equipment like mixing bowls, blenders and measuring jugs and scales, and the many various constituents of enteral feeds are centralized and do not require duplication in every ward. Experience gained improves flavouring and presentation. The dietician also plays an important role in dietary assessment. Her skill will help prevent illogical distinctions being made between "food" and "enteral feeds". The *pharmacist's* role in parenteral feeding is important not only in making additives and mixtures professionally and in ideal conditions, but also in his ability to advise about the compatibility of different mixtures of nutrients and their storage potential. He, like all the clinical personnel, will work in close contact with *bacteriologists and biochemists*. Finally, it is advantageous if a *clinician with a special interest in nutrition* is closely involved. Hospital nutritional treatment should be regarded as a specialty or "special interest" comparable to any other. It is doubtful whether a proper nutritional service within a hospital can ever be supplied *ad hoc*. Increasingly, the advantages of a co-ordinated team of people organizing all nutritional care within a hospital are being recognized. A team approach need not necessarily imply segregation of patients into special units; rather it functions by providing support wherever the patient may be—in the wards, the intensive care unit or, increasingly, even the home.

APPENDIX

CALCULATION OF NITROGEN BALANCE

(After Lee, 1974)

Urinary urea constitutes about 5/6 total urinary nitrogen. Therefore

$$\text{Total urine N(g)} = \text{urine urea (g)} \times 28/60 \times 6/5$$

or

$$\text{Total urine N(g)} = \text{urine urea (mmol)} \times 0.033$$

However, errors are caused if urea accumulates in or is lost from the body pool during urine collection. Since urea is evenly distributed throughout the body water, total body pool can be calculated from plasma concentration, if an estimate of total body water can be made. The formula (total body water = body weight × 60%) can be used clinically.

Nitrogen correction (mg) = change in plasma urea concentration during the urine collection (mmol per litre) × body weight (kg) × 60/100 × 28/60.

Corrections will also need to be made for pathologically high urine or faecal (including fistula) losses—otherwise assume faecal N = 1 g.

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PROCEEDINGS OF THE ANAESTHETIC RESEARCH SOCIETY

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STUDIES OF BODY TEMPERATURE DURING EXERCISE IN HUMAN SUBJECTS SUSCEPTIBLE TO MALIGNANT HYPERPYREXIA

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In a previous communication (Campbell, Ellis and Evans, 1980) we described the effects of food and mild exercise on metabolic rate and various biochemical parameters in human subjects susceptible to malignant hyperpyrexia (MHS). Nine control and nine MHS subjects were studied at rest, fasting, and during 20 min exercise on a bicycle ergometer. Subsequently they consumed a 2510-kJ (600 kcal) liquid meal, rested for 55 min and undertook a further 20-min exercise on the ergometer. Body temperature was measured just inside the rectum at the end of each rest period and at the end of each exercise period.

Rectal temperature was 0.2 °C less in the MHS group at rest fasting, compared with the controls ($P > 0.05$). However, it was significantly less in the MHS group exercising, fasting (0.5 °C, $P < 0.01$), at rest, fed (0.3 °C, $P < 0.05$); and exercising, fed (0.5 °C, $P < 0.01$) compared with controls.

Five MHS and five control subjects, matched for age and sex (mean age 29 yr; four male, one female), rode a bicycle ergometer at six to eight incremental workloads, with no break between each workload, from rest up to exhaustion. The period at each workload was 5 min. Heart rate was measured continuously, and temperatures, which were also recorded continuously, were measured just inside the rectum, in the external auditory meatus, on the lateral aspect of the thigh, on the chest wall just lateral to and above the nipple and on the pad of the thumb. Heart rate after 4 min of exercise at each workload, and mean temperature during the 5th minute of each workload, were used to derive a presumptive temperature for each 10-beat increment in heart rate from 80 to 180 beat min^{-1} for each of the measurement sites.

Mean rectal and thigh temperatures in the MHS group were persistently less than in the controls, but this difference was not significant. Meatal temperature of the MHS group was significantly greater than the control by 0.1 °C at 80 beat min^{-1} and by 0.3 °C at 180 beat min^{-1}. Thoracic wall temperature at 110–160 beat min^{-1} increased by 0.3 °C in the MHS group and by 1.2 °C in the control ($P < 0.05$). Thumb temperatures in both groups at heart rates of 80 beat min^{-1} were similar, but after an initial decrease, thumb temperature in the control group increased steadily throughout exercise. Thumb temperature in the MHS group again decreased with the onset of exercise and remained less than the value at 80 beat min^{-1} until heart rate increased to 130–140 beat min^{-1}. Differences in thumb temperature between the two groups were significant at 110, 120 and 130 beat min^{-1} ($P < 0.05$).

It was demonstrated previously that, at rest and during mild exercise, heat production of the MHS subjects was the same as controls (Campbell, Ellis and Evans, 1980). The differences in temperature at the various sites described must therefore result from an anomaly in the peripheral blood flow in the MHS subject. We postulate that this must involve the sympathetic nervous system.

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SOME OBSERVATIONS WITH DI-ISOPROPYL PHENOL (ICI 35 868)

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Di-isopropyl phenol is a new i.v. anaesthetic available as a 1% solution in 16% Cremophor EL. We have induced anaesthesia in over 200 patients with varying doses of the drug and report some of our findings obtained in unpremedicated adults.

Doses of 1.5 mg kg^{-1} and less, injected i.v. over 20 s, did not induce sleep consistently as judged by cessation of counting. While a 1.75-mg kg^{-1} dose was effective in all patients studied, its effect was very transient and we would recommend 2 mg kg^{-1} as a suitable induction dose. When injected at the peak of reactive hyperaemia (Clarke et al., 1968) this dose caused loss of consciousness in 10.5 ± 0.33 s (mean ± SEM) in 20 patients, indicating that it is a "rapidly acting" drug similar, in this respect, to thiopentone. The onset time averaged 32.5 ± 1.5 s following 2.0 mg kg^{-1} given over 20 s

Pain on injection occurred in 6% of patients in whom there was no extravasation of drug. Table I shows that pain appears to be markedly influenced by the site of injection

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TABLE I. *Frequency of pain on injection*

Vein	Cannula	*n*	Pain
Antecubital	Large	63	1
	Medium	25	1
Hand/wrist	Medium	12	4

A detailed 10–14-day follow-up of the frequency of thrombosis was carried out in 30 patients who received single doses of di-isopropyl phenol into a vein which was not used for any other drug, and in whom arterial pressure recordings were taken in the contralateral arm (Hewitt et al., 1966) Three patients had phlebitis on the 1st or 2nd days after injection and one had localized thrombophlebitis at 14 days. In this respect di-isopropyl phenol is comparable to the barbiturates and Althesin.

Tibial pressure algesimetry (Dundee and Moore, 1960) was carried out in groups of 10 patients following subnarcotic doses of 0.24 mg kg^{-1}, repeated in 3 min, or single doses of 0.5 mg kg^{-1}. In contrast to the findings with thiopentone, ICI 35 868 did not cause any increase in sensitivity to somatic pain and on occasions was followed by slight analgesia. When intermittent doses were given, to a total of 5–7 mg kg^{-1}, analgesia was demonstrated consistently for 10–30 min.

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EFFECT OF SOME GENERAL ANAESTHETICS ON THE ELECTRICAL CONDUCTANCE OF PORE-CONTAINING BLACK LIPID MEMBRANES

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Black lipid membranes (BLM) were formed by applying a bulk lipid solution to a small aperture in a Teflon partition which separated potassium chloride 0.1 mol litre^{-1} aqueous bathing solutions.

In the first series of experiments BLM were formed from a lipid solution comprising glyceryl monooleate and cholesterol dissolved in n-decane. These were made conducting by incorporating the channel-forming polypeptide o-pyromellityl-gramicidin A. Its hydrophylic end group makes it particularly water-soluble, hence reproducible concentrations of polypeptide in the aqueous phase and subsequently the bilayer were readily attainable. For each anaesthetic tested, three different concentrations of o-pyromellitylgramicidin A were used, corresponding to 0.5, 5 and 50 nmol litre^{-1} in the aqueous phase. Anaesthetic was made available to the BLM by equilibrating the bathing solutions and apparatus with a known gaseous concentration of anaesthetic. This obviated the need for specifying bilayer concentrations of anaesthetic and allowed an easy comparison to be made with doses used surgically. In this study the anaesthetic doses were varied between 0 and 4% for halothane, 0 and 2% for methoxyflurane and 0 and 8.5% for diethyl ether (all concentrations are expressed as % vol/vol in the gas phase at 23 °C). None of the anaesthetics tested had any significant effect on the o-pyromellitylgramicidin A-mediated BLM conductance. It would therefore seem unlikely that the primary effect of these general anaesthetics is to cause a significant increase in bilayer thickness (Hendry, Urban and Haydon, 1978).

In order to test if the lack of an effect on channel systems was a more universal phenomenon, the effect of halothane on alamethicin-mediated conductance in BLM formed from a bulk solution of oxidized cholesterol in n-octane was also investigated. The action of alamethicin differs from that of gramicidin by virtue of its conductance being dependent on the applied voltage. Thus a plot of log conductance *v.* the applied potential difference is linear. It was found that 1.8% halothane reduced the gradient of this plot, which at present is interpreted as reduction in the number of alamethicin monomers making up the conducting aggregate.

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ANALGESIC EFFECT OF I.M. AND ORAL KETAMINE

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Ketamine increases pain thresholds at plasma concentrations greater than 100 ng ml^{-1} (Clements and Nimmo, 1981). The duration of analgesia following 0.125 mg kg^{-1} i.v. was less than 5 min, while 0.25 mg kg^{-1} produced analgesia lasting only 5–10 min. Analgesia of this duration has limited clinical application and the present study was designed to assess the analgesic action of ketamine administered orally and i.m

Six healthy, fasting adult volunteers (aged 31.9±(SEM) 2.0 yr, weight 70.7±4.5 kg) were each studied on three occasions at least 1 week apart: twice after ketamine 0.5 mg kg^{-1} (i.m. and oral) and once after placebo. Venous blood samples were taken at intervals for 7 h and ketamine and its metabolites were measured by gas–liquid chromatography.

Pain thresholds were measured by the submaximal effort tourniquet test (Harrison and Bigelow, 1943) carried out at 15-min intervals from 30 min before drug administration until 2 h afterwards. A sphygmomanometer cuff was inflated to 250 mm Hg and the subject squeezed a wrist exerciser once per second. At 15-s intervals he was asked to describe the pain in the forearm on a 0–4 scale (pain score). When the pain was intolerable, the cuff was immediately deflated and the "tourniquet time" noted.

Ketamine prolonged the period of pain-free ischaemic exercise measured at 15 and 30 min after i.m. injection. The mean tourniquet times were 122±8 s and 119±8 s respectively

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(control = 89±3 s and 90±3 s). Thirty minutes following oral administration the tourniquet time was 109±5 s. At all other times, and in the placebo group, tourniquet times and pain scores were similar to the values before administration of ketamine.

All subjects remained conscious and orientated after this dose of ketamine. Following i.m. administration, some light-headedness occurred at 20–45 min.

In the i.m. study, increased pain thresholds were associated with plasma ketamine concentrations of 150 ng ml^{-1} or more. In the oral study, plasma concentrations were only 40 ng ml^{-1} when there was significant analgesia. However, concentrations of the metabolite norketamine were much greater than in the i.m. study and this may have contributed to the analgesic effect.

Clinical trials are indicated to evaluate further the use of both oral and i.m. ketamine in analgesic doses.

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CLOSED-CIRCUIT ENFLURANE USING AN IN-CIRCLE GOLDMAN VAPORIZER

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Despite the manifest advantages of totally closed anaesthetic systems, it remains difficult to predict exact volatile concentrations, particularly with an in-circle vaporizer.

This study examines the inspired and end-tidal concentrations of volatile agent attained in such a system under various conditions. Halothane and enflurane were studied.

The circuit utilized a Goldman vaporizer in the inspiratory limb of a circuit comprising a 1.8-kg soda-lime absorber and two 1067-mm lengths of breathing hose. The patient Y-piece incorporated a McGaw Accutach miniature pneumotachograph head and a side-arm for connection of a Medishield MS 2 mass spectrometer and multiplexer. Simultaneous chart recordings were made of the integrated pneumotachograph output, and the concentrations of oxygen, nitrogen, carbon dioxide and volatile agent measured at the endotracheal tube.

A heterogeneous group of healthy patients was studied in the period before urological surgery. Induction with thiopentone was followed by suxamethonium 1 mg kg^{-1} i.v. The patient's lungs were inflated with a few breaths of pure oxygen, the trachea was intubated and the endotracheal tube connected to the closed circle. Only basal oxygen requirements were supplied.

For IPPV, the bag limb was extended to 2 m and the bag replaced by the patient valve of a Pneupac 2 ventilator. During IPPV the ventilator, which was driven from a separate 400-kPa oxygen supply, doubled as the source of fresh gas, the supply of oxygen to the circle via the anaesthetic machine flowmeter being turned off. In this way the net movement of oxygen towards the circle from the bag limb confined the volatile agent to the circle, which thus remained effectively closed.

The inspired and end-tidal concentrations of volatile were examined at various vaporizer settings, allowing 10 min for equilibration after each adjustment. For both agents the useful range was between settings 1 and 2 on the Goldman vaporizer. The effect of IPPV to 5% end-tidal carbon dioxide was also assessed. Repeatability of attained concentrations in the same patient was found to be good, as judged by the values developed during a period of spontaneous respiration at setting 1½ included both at the beginning and the end of the study.

Inspired halothane concentrations developed under spontaneous respiration agreed with previous work. Setting 1 produced between 0.5% and 0.9%; setting 1½, 1.4–2.4% and setting 2, 3.3–4.5%. Corresponding inspired enflurane concentrations were: setting 1, 0.8–1.4%; setting 1½, 1.9–2.8% and setting 2, 3.7–5%. These values were only marginally increased by IPPV, but end-tidal concentrations were greatly increased by ventilation and the same alveolar concentrations could usually be achieved with a half-stop lower vaporizer setting.

Despite the patients' receiving minimal pre-oxygenation, the maximum concentrations of nitrogen in the circuit never exceeded 56%.

SPINAL ANAESTHESIA WITH HYPERBARIC AND ISOBARIC BUPIVACAINE

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Although bupivacaine has been used extensively in isobaric solution for spinal anaesthesia (Nolte et al., 1977) little is known regarding its use in a hyperbaric solution. In this study we have compared the effects of subarachnoid administration of 0.5% bupivacaine 3 ml in plain solution (isobaric; sp. gr. 1004), with 5% dextrose or with 8% dextrose (hyperbaric; sp. gr. 1016 and 1027 respectively).

Thirty non-pregnant patients undergoing major gynaecological surgery were studied in a "double blind" manner. Each patient received one of the three solutions given in a random order. The spread of loss of sensation and motor power were recorded over the course of 30 min together with measurement of arterial pressure and heart rate. A light general anaesthetic or i.v. sedation was administered subsequently and surgery allowed to proceed. Note was made of the operating conditions and the need for any supplementation to the general anaesthetic.

At the end of operation rapid recovery of consciousness usually occurred and further assessment of the level of sensory loss was made.

The spread of analgesia with both hyperbaric solutions was greater by three to four spinal segments than with the isobaric. Motor block in the legs was complete in all patients in the isobaric group and in nine of the 10 patients in each hyperbaric group. Because of inadequate spread, the isobaric solution was unsuitable for lower abdominal surgery and most patients in this group undergoing laparotomy required an increased halothane concentration or small doses of a muscle relaxant, or both, to provide satisfactory operating conditions. However, the hyperbaric solutions usually produced a block which was adequate for surgery. No difference was noted between the solutions with regard to duration of action. Most of the blocks had regressed to the lumbar segments by 2.5 h.

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PHARMACOKINETICS OF KETAMINE

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Plasma concentration time curves after i.v. administration of ketamine show a biphasic decline with an initial fast slope ($T_{\frac{1}{2}}$ 15 min) followed by a more slowly declining slope ($T_{\frac{1}{2}}$ 180 min). Ketamine pharmacokinetics are the same over a dose range of 0.125–2 mg kg^{-1} and are similar in volunteers and in patients (Clements and Nimmo, 1981). Analgesia is associated with plasma ketamine concentrations of 100–150 ng ml^{-1} (Clements and Nimmo, 1981) and anaesthesia with concentrations of 640–1000 ng ml^{-1} (Idvall et al., 1979). Following induction of anaesthesia with ketamine 2 mg kg^{-1} i.v., recovery of consciousness occurs during the rapid distribution phase. The analgesic effect continues into the slower metabolic phase and the mean plasma ketamine concentration decreases to less than 150 ng ml^{-1} 5 h after administration.

Following i.m. administration of ketamine 6 mg kg^{-1} to three patients, consciousness was lost within 3–5 min and returned approximately 3 h later. The mean peak plasma ketamine concentration of 1970 ng ml^{-1} occurred at 20 min. The mean plasma concentration at 3 h was 623 ng ml^{-1} and plasma concentrations remained greater than 150 ng ml^{-1} 9 h after administration. None of the three patients studied required analgesia after operation whilst the plasma concentrations were greater than 150 ng ml^{-1}. Further studies have been carried out in patients using smaller doses of i.m. ketamine which produced shorter periods of analgesia after surgery.

In six healthy volunteers, ketamine 0.5 mg kg^{-1} i.m. increased pain thresholds for more than 30 min when plasma ketamine concentrations were greater than 150 ng ml^{-1}. The mean peak plasma concentration was 190 ng ml^{-1} and occurred 15 min after administration. The bioavailability of i.m. ketamine was 87%. The mean peak plasma concentration of norketamine was 80 ng ml^{-1} and occurred 1 h after administration. Following oral administration of the same dose of ketamine to the same volunteers, bioavailability was only 15%, presumably resulting from the high "first pass metabolism" of ketamine. The mean peak plasma concentration was only 40 ng ml^{-1} at 30 min after administration. Plasma concentrations of norketamine were much greater (mean peak plasma concentration of 194 ng ml^{-1} at 45 min). Pain thresholds were increased by this dose of oral ketamine. Thus ketamine metabolites must have some analgesic activity, although less than the parent compound.

Ketamine pharmacokinetics are similar in patients and volunteers over a wide dose range. Following i.m. administration, peak plasma ketamine concentrations occur at 15–30 min. Of particular clinical importance is the fact that, in small i.m. doses, ketamine may produce prolonged periods of analgesia after operation.

ACKNOWLEDGEMENT

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EFFECTS OF NITROGLYCERIN-INDUCED HYPOTENSION ON INTRACRANIAL PRESSURE IN DOGS

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There are conflicting reports regarding the pattern of intracranial pressure (i.c.p.) changes produced by nitroglycerin (GTN). Rogers and others (1979) reported that GTN consistently increased i.c.p. during hypotension in cats, whilst Gonzalez-Abola and others (Chestnut et al., 1978) noted only small increases in dogs with a normal i.c.p and no increase in dogs with an artificially increased i.c.p.

In this study, 18 greyhounds were anaesthetized with i.v. pentobarbitone and thiopentone supplemented with an infusion of fentanyl and the lungs were ventilated with an air–oxygen mixture to maintain slight hypocapnia. Following femoral artery cannulation, bilateral cranial burr holes were made. An extradural pressure recording balloon was introduced into one burr hole, and a balloon catheter (capable of being inflated to simulate a mass lesion) positioned in the other. The cranial incisions were closed and made watertight. Rapid i.v. injections of bolus doses of GTN sufficient to produce appreciable decreases in mean arterial pressure (m.a.p.) were given, each injection being administered after m.a.p. and i.c.p. had been stable at control values for at least 10 min. M.a.p. and mean i.c.p. were recorded, both at normal i.c.p. values and after the intracranial pressure had been increased.

At normal values of i.c.p. (<12 mm Hg) hypotension produced an increase in i.c.p. of 3.1 (±0.6) mm Hg (mean + SEM) At increased i.c.p. (12+ mm Hg), dogs with a small reduction in m.a.p. (<25% control) showed an increase of 4.7 (±0.5) mm Hg whereas those with a larger reduction in m.a.p. (>25% control) showed decreases of 3.2 (±0.9) mm Hg in i.c.p In addition, in 58% of observations (11/19) where a decrease in intracranial pressure had occurred, there was a rebound increase as m.a.p. was restored.

Nitroglycerin exerts its hypotensive action mainly by dilatation of the capacitance vessels The resulting increase in brain blood volume may lead to an increase in i.c.p. In situations in which i.c.p. is already increased, dilatation of the cerebral veins is restricted, and a decrease in cerebral blood flow may subsequently result in a decrease in i.c.p. This may modify the reduction in brain perfusion pressure produced during hypotension. However, a rebound increase of i.c.p. as m.a.p. is restored to normal could occur if the rate of restoration of arterial pressure exceeded the capacity of brain autoregulation.

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BEHAVIOUR OF MIXTURES OF ANAESTHETICS AT PRESSURE: SUPPORT FOR THE MULTI-SITE EXPANSION HYPOTHESIS OF ANAESTHETIC ACTION

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In 1978 we presented preliminary data on non-additivity of a mixture of Althesin and nitrous oxide at pressure (Wardley-Smith, Green and Halsey, 1978) which supported some of the predictions of the multi-site expansion hypothesis (Halsey, Wardley-Smith and Green, 1978). This paper reports a more comprehensive series of experiments to test two aspects of the hypothesis: (1) separate sites for different anaesthetics; (2) limited occupancy of these sites.

We used four pairs of anaesthetics: Althesin–nitrous oxide, methohexitone–nitrous oxide, thiopentone–propanidid and thiopentone–nitrous oxide. All were studied in 50% mixtures; in addition two pairs were also used at 25 and 75% mixtures. The dose of one component of the mixture was kept constant throughout the experiment.

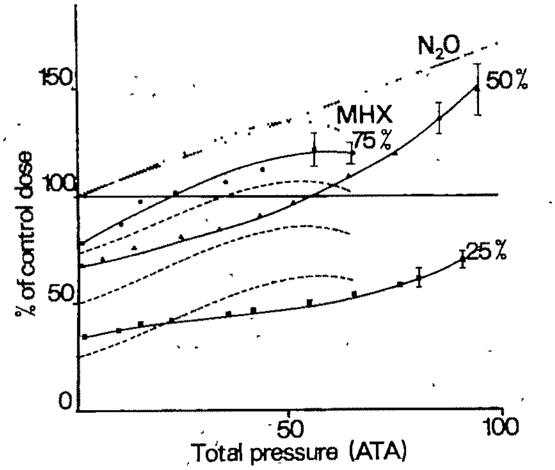

FIG. 1. Pressure reversal data for mixtures of methohexitone (MHX) and nitrous oxide (N_2O): % of control anaesthetic dose required at 1 ATA (AD_{95}) (vertical axis) with varying total pressure in atmospheres absolute (ATA) (horizontal axis). ..... = Pressure reversal characteristics of each agent alone (Halsey, Wardley-Smith and Green, 1978); —— = results for three different mixtures. (In each case 25, 50 or 75% of the control anaesthetizing dose of N_2O was added; MHX was then adjusted until AD_{95} for the mixture was reached. This was expressed as a percentage of MHX required alone at 1 ATA.) ● = "75%" MHX/25% N_2O; ▲ = "50%" MHX/50% N_2O; ■ = "25%" MHX/75% N_2O. ----- = Pressure reversal curves calculated assuming simple additivity at both ambient and increased pressures.

The i.v. agents were infused continuously via cannulated tail veins of male Sprague–Dawley rats (300–350 g). Temperature was maintained at 37 ± 0.5 °C and heart and respiratory rates were measured. Anaesthesia was assessed by noting the response to electrical stimulation. Some examples of the results are shown in figure 1. The 75% methohexitone mixture shows the plateau seen with methohexitone alone, whereas the 50 and 25% mixtures do not. This supports both the existence of separate receptors for these anaesthetics and a maximum occupancy of methohexitone receptors. Similar results were obtained with Althesin–nitrous oxide, suggesting separate receptors, and a limited occupancy for Althesin.

Results for thiopentone–propanidid were not significantly different from calculations of strict additivity, which supports the original prediction of the same receptor for these agents. Results for thiopentone–nitrous oxide showed simple additivity up to 80 ATA, but became more complex at greater pressures.

All these data support the now commonly accepted view that different anaesthetics have separate molecular receptors. They also support the more controversial idea that anaesthetic receptors have only a limited degree of occupancy.

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NON-INVASIVE MONITORING OF BREATHING IN PATIENTS BEING WEANED FROM MECHANICAL VENTILATION

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A decrease in the breath-to-breath variability of tidal volume (V_T), and inspiratory (T_I) and expiratory (T_E) duration has been noted in patients developing respiratory failure (Askanaze et al., 1979).

This study was undertaken to determine if a similar analysis would be of value in monitoring patients being weaned from mechanical ventilation (IPPV). Respiratory movements were recorded in eight patients with respiratory failure in a general intensive therapy unit using an inductance plethysmograph (Hanning, Smith and Ledingham, 1978). The transducer was calibrated for each patient against a dry spirometer or a bag of known volume.

Spontaneous breathing was recorded immediately after cessation of IPPV for periods of approximately 1 h or until IPPV was recommenced. Continuous clinical assessment of the adequacy of spontaneous breathing was made, with intermittent arterial blood-gas analysis. The maximum inspiratory pressure against a closed airway was also recorded. Recordings were repeated at intervals during the period of weaning from IPPV. Each complete record was inspected and undisturbed sequences of 100–400 breath were analysed using a small computer to obtain the mean, standard deviation and coefficient of variation of *V*T, *T*I and *T*E. These were compared with control values obtained in five normal volunteers.

The results obtained show that breath-to-breath variability was reduced in the patients compared with the normal. In individual patients the variability did not correlate well with changes in clinical condition or with the success or failure of weaning.

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DURATION OF ACTION OF I.V. ATROPINE AND METOCLOPRAMIDE AND THE EFFECTS OF THEIR CONSECUTIVE ADMINISTRATION ON THE LOWER OESOPHAGEAL SPHINCTER PRESSURE

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Regurgitation of stomach contents is thought to depend in part on the barrier pressure (BP) between the lower oesophageal sphincter or high pressure zone (HPZ) and the gastric pressure (GP) (Cohen and Harris, 1971). It is therefore important to define the effects on BP of drugs used by anaesthetists.

Although the changes produced by atropine and metoclopramide on the lower oesophageal sphincter have been elucidated (Brock-Utne et al., 1976), there appears to have been no previous study of the duration of action of these drugs, or of the effects of the two drugs administered consecutively.

On three separate occasions, 12 healthy fasted volunteers swallowed a 3-mm diameter silastic tube in which three subminiature strain gauge pressure transducers were embedded at 5, 10 and 15 cm from the tip. GP was recorded and the tube withdrawn with a stationary pull-through technique through the HPZ until all the transducers were in the oesophagus BP between stomach and HPZ was determined. Measurements were repeated at specific intervals following the i.v. injection of atropine 0.6 mg on the first occasion and metoclopramide 10 mg on the second occasion. On the third occasion six of the volunteers received atropine 0.6 mg, followed 10 min later by metoclopramide 10 mg, and the other six were given the two drugs in reverse sequence.

Atropine decreased BP at 5 min from 18.8±1.4 (mean±SEM) cm H_2O to 13.5±1.4 cm H_2O ($P<0.01$) and BP remained significantly less than the control value until recording was discontinued at 60 min.

Metoclopramide increased BP at 3 min from 16.1±1.4 to 21.9±3.0 cm H_2O ($P<0.05$) and a significant increase was maintained until recording was discontinued at 40 min.

The injection of metoclopramide after atropine did not increase BP. The injection of atropine after metoclopramide resulted in a decrease in BP at 5 min from 27.7±4.4 to 16.3±2.9 cm H_2O ($P<0.025$), a value significantly lower than the original BP of 21.7±2.8 ($P<0.05$).

These findings demonstrate that the changes in BP following the i.v. injection of atropine or metoclopramide are maintained for at least 60 min and 40 min respectively, and that atropine abolishes the increase in BP produced by metoclopramide.

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ANAESTHETIC EMERGENCY WORK

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In 1967 an 8-week survey was performed of the emergency workload in three anaesthetic departments: Alder Hey Liverpool, Northampton General and The London Hospital (Taylor et al., 1969). A 6-week follow-up survey was performed at the end of 1978 and the changes noticed at The London Hospital are reported here.

Detailed records were kept of every request for emergency service outside the intensive therapy unit (ITU). Intensive therapy service was recorded "out of hours" only. To diminish exhaustive form filling, the ITU anaesthetist merely indicated if he was working or not for each 15 min of duty.

Although many administrative changes had occurred between the surveys, the number of on-call anaesthetists had remained at five. The time spent on emergencies had increased by 147% during the period between surveys and in 1978–79 the average daily workload was 20.3 h.

Urgent calls (service within 15 min) accounted for 25% of the total service time in 1967, but by 1978–79 these urgent cases occupied 47% of the total time. This was mainly a result of the enormous increase in intensive therapy. The average time spent on intensive therapy in 1978–79 (8.3 h daily) was greater than the total daily emergency commitment in 1967 (8.21 h).

In view of the increased workload from intensive therapy it might appear attractive to reserve staff solely for intensive therapy and cardiorespiratory arrest calls. In order to determine the emergency cover required we tested two deployment options with the aid of Queuing Theory (Taylor et al., 1969b) and computer modelling. The two options tested were:

(1) that an anaesthetist be reserved purely for very urgent cases (priority 1 or 2) and that the others on call serve each request according to urgency and suitability;

(2) that all on-call staff be pooled and requests be dealt with according to urgency and suitability.

The survey data were analysed at 10-min intervals to find the numbers of cases requiring simultaneous service. A computer model based on The London Hospital data was run with the system reduced to two queues (high and low priority) under the pooled resources policy and twice more to determine staff required under the segregated policy.

Using a system of pooled resources an average of 4.45 anaesthetists hourly would be required to maintain the service standards. With the segregated system this figure would be 6.75

In conclusion, there had been an enormous increase in emergency workload between surveys (particularly intensive therapy). The staffing implications are many, but segregation of staff to specific duties would be very expensive of manpower.

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MYOCARDIAL FUNCTION AND CRITICAL CONSTRICTION OF THE LEFT ANTERIOR DESCENDING CORONARY ARTERY: PROTECTIVE EFFECT OF OXPRENOLOL

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Halothane and enflurane both produce significant dose-dependent depression of global and regional myocardial function. These effects are magnified when there is constriction of the left anterior descending (LAD) coronary artery (Cutfield et al., 1980; Francis et al., 1980). Beta-adrenoceptor blocking drugs have been shown to protect the myocardium against the effects of ischaemia (Tomoike et al., 1978). This paper describes the effects of oxprenolol in conjunction with enflurane anaesthesia and critical constriction of the LAD coronary artery.

TABLE I. *Comparison, at 3.3% enflurane, of measurements obtained before and after oxprenolol, expressed as mean % change (± SEM) from values observed at 1.1% enflurane. Critical constriction of LAD was present in both phases.* *$P < 0.05$; *n.s. = not significant*

	Critical constriction	Critical constriction plus oxprenolol
LAD segment end-diastolic length	+7.2 (1.1)	+4.5 (1.6)*
LC segment end-diastolic length	+6.9 (1.0)	+3.7 (1.0)*
LAD segment total systolic shortening	−34.5 (3.2)	−26.2 (6.5)*
LC segment total systolic shortening	−28.1 (6.0)	−25.6 (5.9) (n.s.)
Mean arterial pressure	−41.6 (4.2)	−34.2 (4.1) (n.s.)
LV dP/dt_{max}	−57.3 (4.3)	−53.7 (5.3) (n.s.)
Cardiac output	−49.9 (6.1)	−40.3 (5.2) (n.s.)
Distal LAD coronary artery blood flow	−60.3 (8.3)	−55.0 (10.1) (n.s.)

The responses to increasing concentrations of enflurane in oxygen were studied in six dogs premedicated with morphine 0.3 mg kg^{-1} in a three-phase programme. In the first phase enflurane concentration was increased in steps of 0.55% from 1.1% to 3.3% during controlled ventilation. The second phase involved the application of critical constriction to the LAD artery and the same sequence of enflurane dose increments. In the third phase, oxprenolol 0.3 mg kg^{-1} was given i.v. with critical constriction still applied and the same sequence of enflurane concentrations was followed.

Measurements were made of global cardiac function, (e.c.g., aortic, left ventricular and left atrial pressures, aortic and distal LAD blood flows, LV dP/dt, stroke volume and aortic blood acceleration) and regional myocardial wall motion. Segmental wall motion was measured using ultrasonic length transducers implanted at subendocardial level in territory supplied by LAD and by the left circumflex (LC) coronary arteries respectively.

Critical constriction of LAD artery was applied by means of a micrometer-controlled snare and defined as the maximum amount of tightening of the snare compatible with normal wall motion and causing abolition of the hyperaemic response to a 10-s occlusion of the artery.

Dose-dependent depression of regional and global function was observed in response to enflurane and was found to be more pronounced in the presence of critical constriction of the LAD artery.

After oxprenolol, at 1.1% enflurane, global and regional function were not significantly altered, with the exception of systolic shortening in the LAD territory (+11%). At 3.3% enflurane, regional function was significantly improved in the territory supplied by the LAD artery by comparison with values observed before administration of oxprenolol, as shown in table I. Thus oxprenolol appears to exert a protective effect upon myocardium supplied by a narrowed coronary artery, minimizing the depression of function caused by enflurane. This effect is associated with a modest but not statistically significant improvement in overall cardiac function.

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Br. J. Anaesth. (1981), 53, 191

CORRESPONDENCE

ANTAGONISM OF KETAMINE BY 4-AMINOPYRIDINE AND PHYSOSTIGMINE

Sir,—We read with interest the paper by Agoston and others (1980) demonstrating the ability of 4-aminopyridine to enhance the rate of recovery from ketamine–diazepam anaesthesia in humans. They suggest that 4-aminopyridine is superior to physostigmine in reversing ketamine anaesthesia because of "the indirect vagotonic action of physostigmine, necessitating the additional administration of atropine."

Their assumption that physostigmine can reverse ketamine anaesthesia is probably incorrect. Figallo and Wingard (1979) demonstrated that physostigmine prolonged ketamine-induced sleeping time in rats. We have observed this phenomenon clinically. The mechanism by which this interaction occurred is unclear. The efficacy of 4-aminopyridine in antagonizing the anaesthetic effect of ketamine may be because of antagonistic effects on prejunctional acetylcholine release in the c.n.s.—in a manner similar to that in motor nerve terminals (Lundh and Thesleff, 1977; Amaki, Nagashima and Radnay, 1978).

Physostigmine given in low doses to reverse the residual drowsiness produced by other anaesthetic agents does not always necessitate the administration of atropine. Bidwai and others (1979) have shown that the reversal of diazepam-induced postanaesthetic somnolence with physostigmine 1 mg i.v., did not produce significant vagotonic side-effects, whereas 2 mg did.

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Sir,—We appreciated the article by Agoston and colleagues (1980) on the problem of terminating at will an established ketamine–diazepam anaesthetic by 4-aminopyridine (4-AP). We cannot, however, support these authors' views on pharmacological properties and clinical use of physostigmine.

Because of its specific anticholinesterase (anti-ChE) action, physostigmine will not readily reverse all effects of butyrophenons and diazepines. It might alter the state of consciousness after the administration of these drugs by the extent to which they affect central cholinergic transmission. Any dramatic effect of physostigmine on the effects of diazepam and related compounds has virtually been excluded (Dworacek and Rupreht, 1979; Garber, Ominsky and Orkin, 1979; Rupreht, 1980). From more than 2000 administrations of physostigmine salicylate during the past 6 years, we have found that a dose of 0.04 mg kg^{-1} should be given for optimal central effects. At a rate not faster than 1 mg min^{-1} i.v., there are no vagotonic effects. In most patients the heart rate and arterial pressure increase as soon as the patient establishes good contact with his or her surroundings. We have never needed to give an anticholinergic agent. If it was necessary, however, the drug of choice is methyl-atropine-bromide (MAB) and not atropine-sulphate (AS). The dose-effect curve of the former is highly reliable and superior to that of its sulphate congener. When central effects of MAB were studied, we could not detect any of the well-known effects of atropine on the e.e.g. even when large doses of the drug were administered (Rupreht, unpublished observation). An alternative anticholinergic agent which will hardly affect the central nervous system is glycopyrrolate (McCubbin et al., 1979). We have not used it routinely because it was found to be a potent relaxant of the cardia sphincter (Brock-Utne et al., 1978).

An important point is the administration of 4-AP to a patient who has received neostigmine or pyridostigmine to antagonize tubocurarine. Preliminary reports (A. B. Boidin, personal communication) have warned against such a combination because of the risk of cholinomimetic synergism. Physostigmine, on the other hand, has been given safely to many patients who have received neostigmine.

No reliable treatment has been suggested for 4-AP overdose. In the case of "pure" inhibitors, physostigmine and galanthamine hydrobromide, it is possible to control undesired central or peripheral effects using a centrally or peripherally active anticholinergic agent.

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THE POSTERIOR INTERCOSTAL SPACE

Sir,—Drs Nunn and Slavin (1980) should be congratulated on their excellent study of the anatomy of the posterior intercostal space. However, we feel that their recommendation that the intercostal nerves be injected posteriorly 7 cm from the midline may present two problems. First, in the typical obese patient undergoing cholecystectomy the ribs are felt better more laterally. Second, there have been reports (Benumof and Semenza, 1975; Brodsky and Mark, 1979) of intercostal blocks inserted during operation which have resulted in hypotension consistent with spinal or extradural spread of the local anaesthetic agents. These blocks are generally performed under direct vision at the angle of the rib or more medially.

We therefore recommend (Cronin and Davies 1976) that posterior intercostal blocks are performed about 15 cm from the midline to minimize the possibility of spinal or extradural spread and to ensure that the rib is easily felt to reduce the chance of pneumothorax.

K. D. Cronin
M. J. Davies
Fitzroy, Australia

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HALOTHANE AND OXYGEN ELECTRODES

Sir,—It was stated in a recent article that the effect of halothane on oxygen microelectrodes was reversible only slowly (Maekawa, Okuda and McDowall, 1980). However, the relationship between the time constant of the halothane effect and that of its reversal is unclear. It would be helpful to know the time intervals between exposures in order to qualify the term "slowly". While clarification of the reversal time constant may be of limited significance in the context of bench-type oxygen electrodes, it assumes greater importance when transcutaneous electrodes are considered

Terence D. Rafferty
New Haven, Connecticut, U.S.A.

REFERENCES

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Sir,—It was not our purpose to study the reversal of the effect of halothane on the oxygen electrode and therefore we cannot give a quantitative reply to Dr Rafferty's question.

The high sensitivity to halothane was present again next morning, so we can confidently state that the halothane effect was reversed within 18 h. During the working day there was no sign of reversal and some of the tests were separated by 2 h

D. Gordon McDowall
Y. Okuda
T. Maekawa
Leeds

DOSAGE OF ICI 35 868

Sir,—Rogers and colleagues (1980), in their preliminary investigation of ICI 35 868 1 mg kg^{-1} i.v., failed to induce anaesthesia, contrary to our previous experience (Kay and Rolly, 1977). The onset and duration of sleep induced by this agent is affected by many factors, including premedication, apprehension (which may be increased by extensive monitoring), and especially by rate of injection.

Adam, Glen and Hoyle (1980) showed that, in animals, the half-life of the distribution phase of ICI 35 868 is very short, and this has subsequently been confirmed in man. To induce sleep, the rate of administration must be rapid enough to achieve the brain concentration required in the particular patient and circumstances, allowing for extremely rapid redistribution to other parts of the body. Thus, rate of administration is almost as important as total dosage, and it seems appropriate to use a much shorter injection time than 30 s for clinical use. Even variations in the rate of injection to more than 30 s can affect the onset and duration of sleep produced by a single dose.

ICI 35 868 1 mg kg^{-1} injected over 20 s invariably induced sleep in healthy young unpremedicated patients, and ICI 35 868 and methohexitone were equipotent at a dose of approximately 1.5 mg kg^{-1} (Kay, 1980) It would be unfortunate if unnecessarily large doses of ICI 35 868 became established as a "standard" induction dose.

B. Kay
Manchester
G. Rolly
Ghent, Belgium

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Sir,—As Dr Kay and Professor Rolly have pointed out, the rate of administration is indeed important when analysing the time taken for any drug to induce anaesthesia, and all anaesthetists will be aware of this elementary relationship governing the effectiveness of induction agents. The reason that we chose 30 s as the delivery time for the drug was that the double-blind comparison was with Althesin. To have ignored the recommended injection rate for that drug—30 s—would have been to invite immediate and justifiable criticism.

Now that a strictly controlled initial study is complete, clinical trials of different design and wider scope will determine the range of dose and speed of injection with which the drug should be given in clinical practice.

K. M. Rogers
Glasgow

LUMBAR EXTRADURAL ANALGESIA

Sir,—With reference to the article (Sharrock, 1979) suggesting an anatomical explanation for false positive loss of resistance during lumbar extradural analgesia, the following case may interest your readers.

A distinguished colleague, retired and 75 years of age, required extradural anaesthesia for transurethral prostatic resection. He was of average body build and in good health. With the patient sitting upright, a Tuohy needle was advanced to a depth of approximately 4 cm between the spines of L4 and L5. On removal of the needle stilette, a brief flow of 2–3 ml of clear colourless fluid was observed. Assuming an inadvertant spinal tap the extradural needle was reintroduced at L3–4. Loss of resistance occurred again at about 4 cm. Twelve millilitre of 0.5% bupivacaine was injected slowly but easily; subsequent attempts to introduce an extradural catheter failed.

The patient was asked what sensations had been experienced during the injection of the local anaesthetics. He replied that he had not been aware of the injection and had not experienced any sensation of cold in the back and legs. After a 10-min wait to observe the results of the local analgesic injection, no evidence of motor or sensory blockade could be elicited.

On reattachment of the glass syringe, resistance was again felt on advancing the needle 1–2 mm anteriorly. Further advance of the extradural needle resulted in more definite identification of the extradural space at the expected depth of about 7 cm, confirmed by easy passage of 3 cm of extradural catheter beyond the tip of the needle. Injection of 0.5% bupivacaine 12 ml via the cannula provided excellent analgesia and surgery commenced 20 min later.

On completion of the operation, morphine 2 mg in saline 10 ml was injected to the space via the catheter. On the following day the patient expressed appreciation of the analgesia throughout the operation and had experienced no pain afterwards.

Is this an example of false spinal tap? Did the subject possess two degenerative cavities or cysts within the interspinous ligaments of L4–5 and L3–4, one of which was filled with fluid?

J. W. Downing
Durban, S. Africa

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TORSION OF INNER TUBE

Sir,—A potential hazard of the coaxial breathing system has recently been reported by Inglis (1980) where the inner tube was twisted and no fresh gas flow was delivered to the patient. This problem occurred at least once in this hospital. It was recognized and corrected by untwisting the inner tube and reassembling the system. The manufacturer of this system has not yet found a suitably reinforced tubing which would eliminate torsion and thus will not twist.

I would like to suggest a simpler and much cheaper way of overcoming the problem. If the inner tube at the patient end of the coaxial system is freed, then whenever there is a tendency for torsion, it will rotate at 360° and thus will not twist. In this simple modification a suitable connection can be made which will prevent the inner tube from retracting proximally so that re-breathing will not occur. A modification on these lines was made by our hospital engineer and is in trouble-free use.

N. H. Naqvi
Bolton

REFERENCE

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FLUNITRAZEPAM

Sir,—I read with great interest the paper of Dr Dixon and associates (1980) on i.v. flunitrazepam and i.v. diazepam in conservative dentistry. While many of the points they make are well taken, I wish to comment on the problem of arm pain and venous thrombophlebitis. They used i.v. flunitrazepam 0.014 mg/kg body weight in a solution of 0.25 mg ml^{-1} and 1 week after treatment, arm pain was reported by 13% of the patients. This finding is in accordance with the report by Dundee and associates (1976). We achieved better results using the following method of induction with flunitrazepam:

An i.v. cannula was inserted into a large arm vein. Anaesthesia was induced with a single dose of flunitrazepam 0.015 mg kg^{-1} (elective, premedicated patients) or 0.03 mg kg^{-1} (emergency, non-premedicated patients), diluted with distilled water (0.2 mg ml^{-1}) and given slowly over a period of 1 min. Anaesthesia was maintained with fentanyl and nitrous oxide in oxygen with neuromuscular blockade. All patients were examined on the 1st, 2nd, and 3rd days after operation. The investigation was performed on 800 patients in whom anaesthesia was induced with diluted flunitrazepam and in no case was the occurrence of phlebitis, thrombophlebitis or arm pain recorded. These results suggest that, by using a smaller concentration of flunitrazepam, arm pain and thrombophlebitis can be avoided.

E. Vatashsky
Jerusalem

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APPARATUS FAILURE

Sir,—With reference to Muir and Davidson-Lamb's letter (1980), I have had a similar obstruction of the lumen of a cuffed nasotracheal tube made by Warne Surgical Products, but this occurred after the anaesthesia had been progressing perfectly satisfactorily for approximately 1 h. We do not use non-return inflating valves, so this cannot be the cause of this failure.

C. A. Foster
London

REFERENCE

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TYMPANIC MEMBRANE RUPTURE DURING NITROUS OXIDE ANAESTHESIA

Sir,—We do not agree with Dr Srivastava that nitrous oxide was responsible for rupture of a tympanic membrane during anaesthesia as reported in a recent issue (Srivastava, 1980). Whilst this could be possible theoretically, some further points require clarification.

It has been shown in normal adults that venting of the middle ear during nitrous oxide anaesthesia occurs at pressures ranging from 23 to 42 cm H_2O, and that the rate of increase of pressure with 67% nitrous oxide is about 1 cm H_2O min^{-1}, venting pressure being achieved at between 30 and 40 min (Davis, Moore and Lahiri, 1979).

The pressure required to rupture a normal tympanic membrane is not, to our knowledge, recorded, but pressure differences between the middle ear and external auditory meatus in the region of 200 cm H_2O will occur whilst swimming at a depth of 2 m or travelling in a civil aircraft with a cabin altitude of 8000 feet if venting is prevented by malfunction of the eustachian tube. Such activity, whilst it may be associated with discomfort, is not assosciated with barotrauma in the absence of pre-existing ear disease.

The fact that the patient was in good health with no past history of ear problems or earache would suggest that venting would not be impeded, and so such pressure would not be achieved.

Also, the time from onset of nitrous oxide administration to the discovery of blood in the external auditory meatus is of significance. One would not expect pressures capable of tympanic membrane rupture to be attained for well over 40 min.

As alcuronium was given for intubation, the lungs were presumably ventilated for a few minutes using a face mask. This, if applied in the presence of respiratory tract obstruction, as may result from position or continuing muscle tone, may cause an increase of pressure in the nasopharynx which would force gas along the eustachian tube.

Whether the pressures attained in the middle ear would be sufficient to cause rupture of the tympanic membrane would depend upon the force used to squeeze the reservoir bag.

J. A. Carter
F. M. Nofal
Bristol

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Davis, I., Moore, J. R. M., and Lahiri, S. K. (1979). Nitrous oxide and the middle ear. *Anaesthesia*, 34, 147.

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BOOK REVIEWS

Parenteral and Enteral Nutrition—A Practical Guide. By G. D. Phillips and C. L. Odgers. Published (1980) by Flinder's University, South Australia. Pp. 105; illustrated; indexed. Price A$8.75.

This small monograph of 95 pages, including appendices, was developed from notes on "Parenteral Nutrition and Gastric Tube Feeding" written in 1977 as guidelines for the staff of Flinder's Medical Centre. The authors emphasize their intention of providing a clear safe practical guide for the "non-expert" and accordingly the text is concise and necessarily didactic. The subject matter is divided into 26 brief chapters, some of which are little more than expanded paragraphs, but which contain a surprising amount of information supplemented by references in areas of controversy.

The first 10 chapters encompass Perspective, Logistic Considerations, Indications and Contra Indications, Venous Access and Dietary Component Requirements. These are followed by chapters on Complications, Monitoring and a more contentious section on the Role of the Nurse. Chapters 14–16 refer to parenteral nutrition in specific disease states and in the home and chapters 17–21 describe the pharmacological aspects of the preparation of solutions and the problems associated with the maintenance of sterility and additive compatibility. The text then concludes with short sections on Protein Sparing Techniques, Nutritional Assessment, Paediatrics and Enteral Comparisons.

While undoubtedly there are points of criticism in the recommended techniques—for example catheters should never be introduced through needles—and disagreement over some aspects of the text, there is still a great deal of valuable practical advice offered to the reader. Of particular merit is the emphasis on the role of the pharmacist in the aseptic preparation of correctly balanced solutions and the concept of the parenteral nutrition team.

Unfortunately, as the book was aimed at Australian readers, many of the products mentioned are irrelevant to British practice; nevertheless, the fundamental principles remain unchanged and for its price it remains good value as a basic primer.

Winifred E. I. Finlay

Obstetric Clinical Care. Edited by J. S. Crawford, J. B. Weaver and R. J. Wilday. Published by Elsevier/North-Holland Biomedical Press. Pp. 417; illustrated. Price £32.25.

This book is a review of the proceedings of the first European Congress of Obstetric Anaesthesia and Analgesia which was held in Birmingham in September 1979, and does justice to a first class meeting. It provides an excellent balance between presented material and discussion, which is probably in no small way a result of the unusual format of the meeting. Following the presentation of three papers, the audience split into groups of approximately 30 people under a chairman to discuss these papers. Points from these discussions were then referred back via the chairmen to the original speakers at the end of the session.

The meeting was concerned with the clinical care of mother and baby rather than with presentation of recent research. The subjects included relief of pain in labour, anaesthesia for operative obstetrics, ante-natal care, neonatal resuscitation and intensive care of mother and neonate. These topics were discussed by anaesthetists and by other specialists—a physiotherapist, midwives, obstetricians, paediatricians and an intensive care physician. The result is an up-to-date review of current clinical practice. Indeed, throughout the book the mulitdisciplinary nature of the subject and the need for close co-operation between disciplines, is stressed.

The book was produced relatively quickly, and this may account for a number of irritating spelling mistakes and the occasional obvious misprint—"hyp*er*tension should be treated with ephedrine". Some of the forms of therapy advocated are unlikely to gain favour in this country, for example the use of propanidid to relieve pain in the late stages of labour. These criticisms are very minor and the editors are to be congratulated on producing an up-to-date summary of clinical practice which should be in the library of all departments involved with the perinatal period.

M. Morgan

Obstetric Analgesia and Anaesthesia. Monographs in Anaesthesiology No. 7. By G. F. Marx and G. M. Bassell. Published (1980) by Elsevier/North-Holland Bio-Medical Press. Pp. 415; illustrated; indexed. Price $75.50.

This book is the latest addition to a group of several texts published since 1975 on obstetric analgesia and anaesthesia. Its stated aim is to provide an overview of this field for all members of the obstetric care team, but particularly for obstetric anaesthesia residents, registrars and fellows. Twelve of the contributors work in the U.S.A. and six work this side of the Atlantic. Much of the information in the book is available in the other texts, but there are differences both in the presentation of material and in the selection of references.

There are 34 pages on the "physiologic considerations of the mother" and a further 76 pages concerning uterine, placental and neonatal physiology. Normal maternal arterial carbon dioxide and oxygen tensions are given as 32–33 torr and 106–108 torr respectively, quoting "Andersen et al (1969)" in the text, but giving "Andersen and Walker (1970)" in the list of references at the end of the chapter. Andersen's blood samples were taken after the patients had been resting in the supine position for 5 min. It would perhaps have been better to have quoted the figures of Templeton and Kelman (1976), and presented them in relation to gestational age.

In the part on general anaesthesia for Caesarean section a favoured induction procedure was a sequence of ketamine 0.4–0.5 mg kg^{-1} followed by thiopentone 2 mg kg^{-1}. The use of the head-up position combined with cricoid pressure was recommended.

Inability to intubate the trachea is discussed in a 43-line section under complications, but it is not indexed under any of the expected headings. The treatment recommended for overcoming intubation difficulty from oedema of the laryngeal mucosa is to select an endotracheal tube 0.5–1 cm smaller in diameter! Failure or difficulty with intubation is mentioned several times in the chapter dealing with maternal mortality. The procedure recommended for an unexpected failure to intubate is to allow the mother to regain consciousness. A step-by-step account of any manoeuvres which might make this process a little safer is not outlined.

An overview of a large subject will inevitably not satisfy every reader. There may be either a lack of fine detail related to his special interest, or a lack of information on specific problems or technical procedures considered to be of immediate concern. On the other hand, there may be a good account of a technical procedure which is not normally his responsibility. An example of this in the book is an account of how to obtain a satisfactory sample of blood from the fetal scalp.

Overall, the book is a valuable addition to the literature concerned with obstetrics and anaesthesia. It can be recommended to all anaesthetists who are involved with obstetrics. It is a book for reading rather than ready reference.

M. E. Tunstall

REFERENCE

Templeton, A., and Kelman, G. R. (1976). Maternal blood-gases ($P_{A_{O_2}} - Pa_{O_2}$), physiological shunt and V_D/V_T in normal pregnancy. *Br. J. Anaesth.*, 48, 1001.

Obstetric Anaesthesia and Analgesia, 2nd Edition. By Donald D Moir. Published by Baillière Tindall. Pp. 326, illustrated; indexed. Price £12.50.

This is the second edition of a book that first appeared in 1976. The format remains unchanged and retains the excellent summary on the modern management of pregnancy and labour by M. J. Carty.

During the 4 years since the appearance of the first edition, new and improved methods of measurement have increased our knowledge of the effects of many drugs and anaesthetic techniques on placental blood flow and the welfare of the fetus at birth. This new information has resulted in the revision of all chapters, some having been extensively re-written. This particularly applies to the section on regional analgesia, where the advantages of an extradural block to mother and fetus are repeatedly stressed, as are the harmful effects of inferior vena cava occlusion. The obvious advantages of spinal analgesia for such manoeuvres as forceps delivery are pointed out. The techniques of performing the various regional blocks are clearly described. The chapters on general anaesthesia and selection of anaesthesia for various obstetric procedures are quite excellent. The former presents a balanced view of the requirements and problems of any general anaesthetic technique for obstetric surgery, while in the latter the arguments for increasing use of extradural analgesia for Caesarean section are clearly presented. This chapter contains a section on the problems of anaesthesia for termination of pregnancy, and also evaluates the position of ketamine in obstetrics. The complications encountered in obstetric patients, such as pre-eclamptic toxaemia, amniotic fluid embolism and bleeding disorders, and those of general anaesthesia, for example Mendelson's syndrome, and their management are discussed in a separate chapter, which also contains an informed discussion on the problems and management of the patient with heart disease in labour.

The author has a refreshing style of writing that makes for easy reading, and which also no doubt contributes to the fact that this second edition has increased in length by only 33 pages. The simple line drawings are clear and informative. Each chapter is accompanied by a large number of up-to-date references, and there is a very good index.

Dr Moir states in the preface that the book was written for the practising clinical anaesthetist and examination candidate, but he is being modest in this claim. The book represents a first class summary of the present state of the art and should be in the possession of all anaesthetists concerned in any way with obstetric patients. In addition, it will benefit obstetricians and paediatricians and is essential reading for examination candidates. The book is surely destined to become a standard work on the subject and is highly recommended.

M. Morgan

Anaesthesia for Orthopedic Surgery. Edited by H. L. Zauder. Published by F. A. Davis Co., Philadelphia. Pp. 229; illustrated; indexed. Price $37.50.

Aspects of anaesthesia for all types of orthopaedic surgery are dealt with in this volume, as its title suggests. There are also chapters on related topics highly relevant to the anaesthetist, such as fat embolism. Some contributions seem outside the scope of the title and might be omitted as they are dealt with elsewhere more fully. These include chapters on "Early Mobilisation of the Severely Injured Patient", "Massive Blood Replacement" and "Haemophilia".

The text throughout is readable, but tends to be verbose. Lack of tabulated summaries also make reading tedious and the illustrations could be better. References are plentiful, although not entirely up-to-date. There is perhaps an over-emphasis on associated medical and orthopaedic problems with, for example, 22 pages of a 30-page chapter on fractured neck of femur devoted to various problems of the elderly (for example cardiac disease). However, the section on rheumatoid arthritis in the chapter on total hip replacement is excellent and most useful.

The contribution on regional anaesthesia of the limbs from Dr Alon P. Winnie is refreshing, with many original details of technique and a most helpful discussion section.

In summary, a cautious welcome to this book, which would be better if pruned and the presentation improved.

P. J. McKenzie

Laryngeal Biomechanics. By R. Fink and R. J. Demarest. Published by Harvard University Press, Cambridge. Pp. 134; illustrated; indexed. Price £21.00.

This book results from co-operation between the ever-versatile Professor Fink and Robert Demarest who is Head of the Department of Medical Illustration at Columbia University, College of Physicians and Surgeons. One would therefore expect it to have a high standard of writing and illustration. It has. It is, indeed, beautifully produced with very few typographical errors and with a wealth of half-tone sketches, drawings, diagrams and radiographs. It is a pleasure to handle and peruse.

The publishers' description is fair and accurate: "In separate chapters the authors consider the functions of the larynx—as a safeguard for the free passage of air, to protect the airway from invasion, as a plug that resists expiration during effort, and as the instrument of speech and song.... The laryngeal tissues are seen as folding and unfolding in response to respiratory excursion of the trachea, action of the intrinsic and extrinsic laryngeal muscles, the respiratory air current, and the elastic recoil of ligaments, membranes and articular capsules."

The format of the book is unusual in that each chapter is made up of two separate parts. The first is a relatively short text with many references to illustrations throughout the book. The rest consists of the many illustrations which are primarily relevant to that particular chapter, but each with such generous captions that this section almost makes a text in itself. It would perhaps be appropriate for the clinical anaesthetist to look through these illustrations, whereas the person with a true, detailed interest in the larynx could settle to the much more demanding process of reading and correlating fully. He would become much better informed thereby and also be stimulated by comments on such things as the importance of ossification of the thyroid cartilage to the performance of Olympic swimmers, and the anatomical reason why a chimpanzee cannot whisper.

E. A. Cooper

Anaesthesia and Neurosurgery. By James E. Cottrell and Herman Turndoff. Published (1980) by C. V. Mosby, St Louis. Pp. 433; illustrated; indexed. Price £32.50.

Anaesthesia and Neurosurgery is a beautifully presented and referenced book in which the editors have succeeded in recruiting thirty of the world's leading neurologists, neurophysiologists, neurosurgeons and anaesthetists. Chapters on basic physiology cover Cerebral and Spinal Cord Blood Flow, Brain Oxygen Consumption and Cerebrospinal Fluid Mechanisms. Although there are places where the reader is led through the literature at a feverish pace, general common sense prevails with clear concluding comments and emphasis on the clinical implications. Chapters on Intracranial Pressure Monitoring and Interpretation and Intracranial Pressure Control repeat the anatomy and history and generally stress the importance of intracranial compliance in contrast to cerebral perfusion pressure. Intracranial Pressure Control is dealt with in a particularly verbose and unreadable manner and contains numerous dubious statements: "Many herniating patients are already hyperventilating and sufficiently hypocarbic so as not to benefit from passive hyperventilation." On the use of an extradural blood patch: "We have no experience with this therapeutic technique and are not enthusiastic about its use for theoretical reasons. Blood is a noxious substance, and the accidental injection of blood into the subarachnoid space may produce a severe inflammatory response."

There is an excellent chapter on Neuroradiology, then the chapter Anaesthesia for Supratentorial Tumours repeats the neurophysiology and loses clarity in a welter of information. Posterior Fossa Surgery is described with the sitting position as frequently used in North America. Bruce gives a dogmatic but clear exposition of a neurosurgeon's view of the management of severe head injury and Matjasko reviews exhaustively the Peripheral Sequelae of Head Injury.

Barbiturate protection of the brain has a chapter which provides no clear clinical advice. Jennett and Karion have written realistic, if depressing, reviews of coma and brain death.

Chapters on Intensive Care, Mechanisms of Injury and Treatment of Acute Spinal Cord Trauma, Hypotensive Anaesthesia and Neurophysiologic Evaluation—or more accurately Evoked Potentials—complete the rather Curate's Egg pattern of this book.

Anaesthesia and Neurosurgery is too incomplete to be a textbook, as it lacks discussion on several major problems, such as hypophysectomy, paediatric neurosurgery and pain therapy. Nevertheless, many excellent reviews of aspects of neuroanaesthesia are provided and will make rewarding reading for clinicians, especially those familiar with neurosurgical anaesthesia.

R. Greenbaum

The Circulation in Anaesthesia: Applied Physiology and Pharmacology. Edited by C. Prys-Roberts. Published (1980) by Blackwell Scientific Publications. Pp. 642, xii, illustrated, indexed. Price. £32.50.

The first anaesthetic death was almost certainly a consequence of ventricular fibrillation following the combination of fear, catecholamines and chloroform. Since then one major role for anaesthesia has been to keep the patient alive as well as anaesthetized. Disorders of the circulation are common causes of problems for the anaesthetist who must have a good knowledge of the relevant physiology, pathology, pharmacology and assessment systems if he is to give the best service for his patient. In this book Professor Prys-Roberts has drawn on his own extensive knowledge and gathered a team of 19 authors to provide a source book of the applied physiology, pharmacology and clinical measurement of the circulation.

Over half the book is devoted to the applied physiology, beginning with a section on the heart. I particularly enjoyed Ty Smith's review of myocardial function and anaesthesia which points out the problems of assessing "contractility". Other sections deal with the peripheral circulation, special circulations to the brain, the kidney, the splanchnic bed and the lungs. The effects of ventilation and of anaemia are considered in detail. Readers will find the pattern of the physiological description followed by a consideration of the effects of anaesthetic drugs and techniques easy to follow.

The second section looks at the pharmacology of the circulation, dealing with the adrenergic system, the cholinergic system, the effects of inhalation and i.v. anaesthetics and the use of drugs to produce hypotension. These are good reviews, but I missed not having specific chapters on the treatment of arrhythmias, heart failure and hypertension.

The final chapters deal with invasive and non-invasive measurement of the circulation and with electrical hazards. These are useful guides; it would help if more authors of scientific papers knew the reliability of their instrumentation.

Prys-Roberts states that the book is designed to provide the medical student, the postgraduate anaesthetist and the seasoned veteran with an up-to-date account of the circulation in anaesthesia. It will probably be too comprehensive for the undergraduate and, because of some omissions, too restricted as the sole source of information for the trainee anaesthetist. The seasoned veteran will certainly admire the quality of these reviews and gain fresh insights into his work. He may also be led to try to fill some of the many gaps in our knowledge of the effects of anaesthesia on the circulation. What does become apparent is the lack of knowledge we have in so many fields. If the veteran feels confused, he has some responsibility to provide better information. This book is an excellent source from which to start as all chapters carry good reference lists.

As always with this publisher, the book is a delight to read. There are two small criticisms: the index is not up to standard and the text always refers to epinephrine, not adrenaline. Surely, in books produced in the United Kingdom, B.P. names are more appropriate. I recommend this volume to all anaesthetists with interests in the circulation. It should be available to all postgraduate students in their libraries.

John Norman

Acupuncture in Medical Practice. By Louise Offendal Wensel. Published (1980) by Reston Publishing Company Inc., Beston, Virginia, U S A. Pp. 335; Illustrated; indexed. Price £10.35.

Acupuncture is probably not a viable alternative to modern anaesthesia for patients undergoing surgery. However, it may have a place in the management of chronic illness or intractable pain which are not responding to more conventional measures. Unfortunately, much available literature is based on translation of oriental works and steeped in mysticism and folk lore This well-produced book is an attempt to redress the balance and determine the place of acupuncture in American medicine.

Dr Wensel has had considerable practical experience in this field and gives a clear and detailed account of the theory and practice of acupuncture, based on traditional Chinese medicine, with classical meridians and specific acupuncture points. This is followed by a balanced discussion on differences in Chinese and Western concepts and an examination of the role of this ancient art in current medical practice. It is refreshing to see a lengthy discourse on relevant neurophysiological and biochemical mechanisms in the understanding of its known analgesic and regulatory effects on various systemic diseases. There are numerous, up-to-date references to the literature but notable omissions, such as the important review by Nathan (1978) on acupuncture analgesia. Dr Wensel comes to the conclusion, with which most of us would agree, that acupuncture is comparatively safe and inexpensive, but that its use should be confined only to properly investigated and diagnosed chronic disorders for which no other effective remedy is available. This is certainly true of chronic pain, but greater emphasis could have been placed on the fact that its value is more as an adjunct than as the sole therapeutic approach. The second half of the book, covering more than 100 pages, is less satisfactory. It describes the acupuncture treatment of specific conditions with an uncritical review of its effects in a whole host of assorted physical, neurological and psychosomatic disorders. The author has wide experience, but it is difficult to reconcile these claims with her more scientific approach to organized clinical research and possible acceptance of the skilled acupuncturist in modern health care. The book ends with a list of trite questions, to determine how thoroughly its contents have been perused, which is more likely to irritate than amuse the average British reader!

Acupuncture in Medical Practice is well produced with clear print and more than 30 detailed drawings of the location of specific acupuncture points. Illustrations of needles and equipment might have been helpful but are not provided. The book contains much useful information for anaesthetists in pain relief clinics, research workers and others interested in the technique and application of acupuncture.

Mark Mehta

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Topical Reviews in Anaesthesia, Vol. 1. Edited by J. Norman and J. Whitwam. Published (1980) by John Wright and Sons Ltd, Bristol. Pp. 271; illustrated; indexed. Price £13.50.

When one is presented with yet another review one is always tempted to question the need for it. Reviews appear in increasing numbers and, with such terms as review of reviews now appearing, one wonders if there should not be a review non-proliferation treaty. However, the law of supply and demand presumably indicates that these reviews are purchased in a significant number, even if few actually read them.

Topical Reviews in Anaesthesia, of which this is the first volume, is, however, one of the best conceived of the reviews which have recently become available. It contains four separate articles on the mechanisms of general anaesthesia (C. D. Richards); on the mechanisms of local anaesthesia (B. G. Covino); on transfer of drugs across membranes (Felicity Reynolds); and on anaesthesia for cardiac surgery (J. M. Manners). The first three can broadly be described as being concerned with theory and the last with practice.

In each of the first three reviews the reader will find much material which, although of fundamental importance to the theory of anaesthesia, has not yet become generally available in the anaesthetic literature. For example, the effect of general anaesthesia on membrane fluidity has been debated for nearly a decade, but this is probably the first time in which there has been a clear and authoritative explanation available to the practising anaesthetist. Other examples, too, could be given from the chapters on local analgesia and the transfer of drugs across membranes.

It is no use pretending that the first three chapters are easy going. To those whose knowledge of, for example, physical chemistry has grown rusty over the years the material will be understood only with considerable difficulty and close study. Nevertheless, just as it has been said that poetry can communicate without being understood so, too, the average anaesthetist will be able to get the gist of the message even if some of the argument is difficult to understand.

The last review in this book is concerned with the craft of anaesthesia—of one of the more exacting of its branches. J. M. Manners' article on anaesthesia for cardiac surgery brings the reader up with a jolt. The abrupt (almost harsh) transition from what is largely scientific to what is largely clinical serves to emphasize the differences between the two and gives the impression, almost, of having been added as a sop to those who might find the previous articles too difficult to understand. This is not to say that the final article is not a good one of its kind and there is, of course, no doubt that it is the chapter in which the practising anaesthetist will find himself most at home.

There is an excellent list of references which would certainly serve someone who is interested in going more deeply into the subjects concerned or even embarking in research into them. All in all this is an interesting and stimulating book.

J. E. Utting

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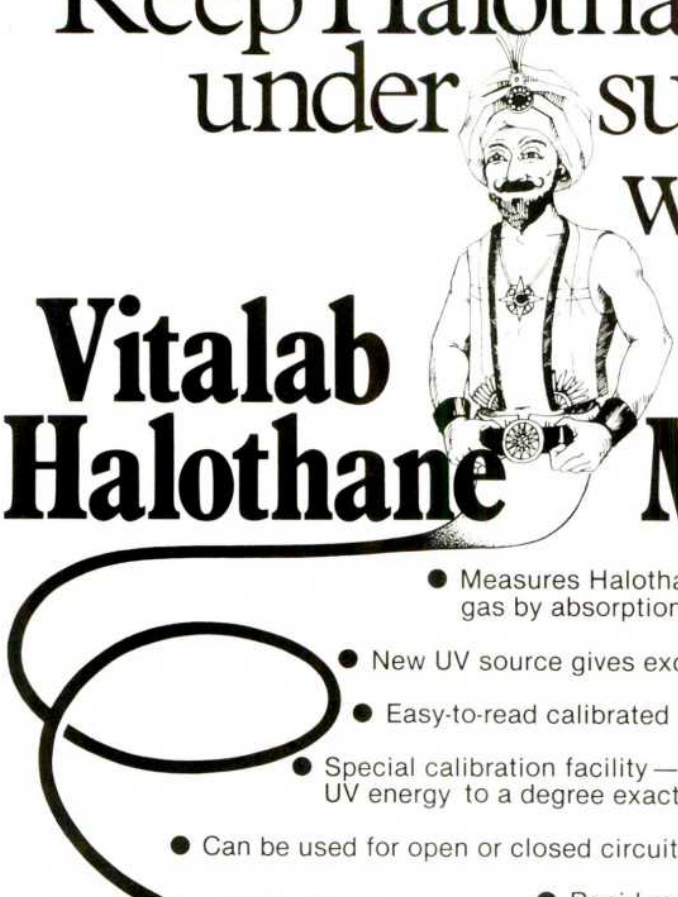

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several minutes (7.7±0.6 SEM) and was propagated to the jejunum but not the ileum. Thiopentone did not stimulate the antrum nor alter the frequency of the basal electrical rhythm (BER) in the small intestine (fig. 2). The stimulation was abolished when thiopentone was preceded by either atropine 0.05 mg kg^{-1} or pentolinium 0.2 mg kg^{-1} (six separate recordings, three dogs) (table I). Ketamine 8 mg kg^{-1} had no effect on the resting interdigestive mechanical or electrical activity, but when thiopentone (six separate recordings, three dogs) was administered after ketamine, significant ($P<0.001$) stimulation of mechanical and fast spike electrical activity still occurred. Minaxolone 2 mg kg^{-1} also caused significant stimulation. The minaxolone injection was followed within 2 min by the onset of mechanical and fast spike activity ($P<0.001$) (three dogs, five separate recordings) but did not alter the BER. The fast spike electrical and mechanical activity following minaxolone did not occur after injection of atropine 0.05 mg kg^{-1} or pentolinium 0.2 mg kg^{-1} (three dogs, five separate recordings).

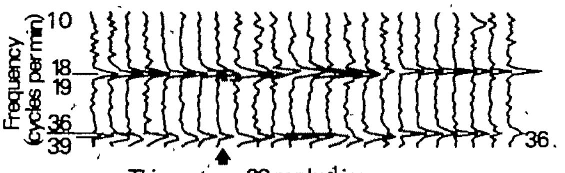

FIG. 2. Fast Fourier Frequency Analysis of BER recorded from electrodes attached to the duodenum. The BER primary frequency is seen to be unchanged (18–19 cycles per min).

TABLE I. *Effect of thiopentone on the frequency of fast spike electrical activity recorded from electrodes attached to the duodenum. The effect of atropine and pentolinium on fast spike activity after injection of thiopentone is also shown*

I.v. anaesthetic	Spikes per min (±SEM)	Duration of stimulation (min ±SEM)
Thiopentone 20 mg kg^{-1}	92±10	7.7±0.6
Atropine 0.05 mg kg^{-1} followed by thiopentone 20 mg kg^{-1}	0	0
Pentolinium 0.2 mg kg^{-1} followed by thiopentone 20 mg kg^{-1}	0	0

DISCUSSION

The interdigestive migrating myoelectrical activity consists of a burst of intense electrical spike activity (phase III) which migrates from the stomach to the ileum. This activity fades out at the ileocaecal junction and is replaced by a further burst of activity starting at the stomach. The intense activity persists for about 5 min at a single recording site and takes 110 min to travel to the small intestine (Szurszewski, 1969; Carlson, Bedi and Code, 1972). At a given recording site intense activity is preceded by a period of intermittent spiking activity (phase II) and followed by a period in which fast spike activity is absent (phase I). Therefore, the activity front (phase III) passes the duodenal recording site before it arrives at the jejunal recording site. Thus, the duodenal recording site may exhibit phase I activity and the jejunal recording site, simultaneously, phase II activity, while between these recording sites lies the phase III activity front.

Thiopentone stimulated intensely the canine duodenum and jejunum, but not the antrum or ileum when given as a bolus injection. The intensity of activity was similar to that seen during phase III of the migrating myoelectrical complex. Stimulation occurred within 2 min. In all the experiments the thiopentone was injected at a comparable time in the interdigestive cycle, during phase I in the duodenum and phase II in the jejunum. There was no evidence that thiopentone acted differently during the two phases. The degree of stimulation was similar at each recording site. There was, however, a delay between the onset of stimulation such that stimulation occurred initially in the duodenum and was propagated to the jejunum (fig. 1). There was no propagation to the ileum. The frequency of the duodenal and jejunal BER was not altered by thiopentone.

It has been suggested that thiopentone possesses a peripheral parasympathomimetic effect on bronchi (Adriani and Rovenstine, 1943), but in the intestine, the stimulation was inhibited not only by atropine but also by pentolinium, which suggests a central effect. Stimulation of intestinal motor activity is characteristically parasympathetic, whereas inhibition is sympathetic in origin. Therefore, it is of interest that ketamine, which has a sympathomimetic action, did not stimulate the

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INFLUENCE OF SUXAMETHONIUM ON THE POTENCY OF ORG NC 45 IN ANAESTHETIZED PATIENTS

N. KRIEG, H. H. L. HENDRICKX AND J. F. CRUL

SUMMARY

The non-depolarizing neuromuscular block produced by Org NC45 was potentiated by the previous administration of suxamethonium 1 mg kg^{-1}, shown by twitch depression of 91.3 ±2.4% when the same dose of Org NC 45 was administered after recovery from suxamethonium compared with the control value of 71.9 ±6.5%. The recovery index was also prolonged from 8.1 ±0.3 to 10.4 ±1.0 min after suxamethonium. The dose–response curves for Org NC 45 showed a 1.66 potentiation factor for ED$_{50}$ and 1.73 for ED$_{95}$, caused by the previous administration of suxamethonium. This interaction is likely to occur in the plasma

The influence of depolarizing muscle relaxants on the potency and duration of subsequently injected non-depolarizing neuromuscular blockers has been reported frequently. Foldes and colleagues (1957) observed potentiating effects after suxamethonium infusions on tubocurarine in dogs and cats (Foldes et al., 1957). Katz and others (1969) and Katz (1971) partly confirmed these findings in man. Walts and Dillon (1969) found the opposite for tubocurarine and Walts and Rusin (1977) reported no significant influence for pancuronium. Krieg, Crul and Booij (1980) found such an interaction between suxamethonium and the new non-depolarizing relaxant Org NC 45. We have studied its effect in more detail.

METHODS

Twenty-eight healthy female patients undergoing laparoscopic sterilization (23) or elective abdominal surgery (5) gave informed consent for the study. The body weights ranged from 48 to 84 kg (66 ±2, mean ± SEM) and the ages from 18 to 58 yr (38 ±2). Premedication consisted of atropine 0.25 mg, droperidol 5.0 mg and piritramide 0.15 mg kg^{-1} given i.m. 45 min before induction of anaesthesia.

Induction of anaesthesia was with thiopentone 5–6 mg kg^{-1} and fentanyl 0.1–0.2 mg i.v. and anaesthesia was maintained with 67% nitrous oxide in oxygen. Small incremental doses of fentanyl 0.05 mg and thiopentone 25 mg were added as needed. The right ulnar nerve was stimulated via subcutaneous thin-wall needle electrodes (22 gauge) near the wrist. A Grass S 88 nerve stimulator delivered square-wave pulses of 0.2 ms duration at 0.1 Hz with supramaximal amplitude. Contraction force of the corresponding adductor policis muscle was measured using a Statham UC 3 force displacement transducer and recorded on a polygraph.

Bolus injection of Org NC 45

Twenty-three patients were randomly selected from the total, and allocated to two groups. After induction of anaesthesia, in group I ($n = 10$) the trachea was intubated with the aid of suxamethonium 1 mg kg^{-1}. After complete recovery from the depolarizing block, a bolus of Org NC45 36 μg kg^{-1} was administered i.v.

In group II ($n = 13$) the same dose of Org NC 45 was given without suxamethonium and the trachea was intubated at maximal twitch depression.

The time from the end of injection to the maximum effect (onset), the time to recovery of 90% of control twitch tension (duration 90), and the time of recovery from 25 to 75% of control twitch tension (recovery index) were compared in both groups.

Titration of the cumulative dose–response curve

In the remaining five patients we obtained a cumulative dose–response curve of Org NC 45. After induction of anaesthesia the trachea was intubated under local anaesthesia (lignocaine 10%

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HEXOBARBITONE DISPOSITION AT DIFFERENT STAGES OF INTENSIVE CARE TREATMENT

I. RIETBROCK, G. LAZARUS, E. RICHTER AND D. D. BREIMER

SUMMARY

The pharmacokinetics of hexobarbitone were investigated in 22 patients in an intensive care unit. The results were compared with those obtained in a healthy group for three time periods· 3rd or 4th day (I), 5–8th days (II) and 13–29th days (III) of treatment. Hexobarbitone 7.32 mg per kg of body weight was administered by i.v. infusion in 60 min. At the end of the infusion, the mean plasma concentration of group I was 71% greater than control group, groups II and III were near to control. In all patients the post-infusion concentration–time course of hexobarbitone could be described by two-compartment kinetics. The biphasic decrease in plasma concentration of hexobarbitone was more rapid in groups II and III, than in either the control group or in group I. At the beginning of treatment patients generally showed an unchanged hexobarbitone half-life, a slightly decreased plasma clearance, a reduction of approximately 50% of the initial distribution volume (V_1) and a reduction of 44% of the distribution volume at steady state. In groups II and III the mean of these values were comparable to control. However, plasma clearance had increased by about 87% in group II compared with control, and after 2–3 weeks (group III) by about 143%. Correspondingly, half-life was reduced by 45% and 58% respectively. The pharmacokinetics were not related to change in liver function. The presence of clinical and bacteriological signs of septicaemia was closely associated with an enhanced hexobarbitone clearance.

Duration of stay in hospital and the use of medication increase with the severity of the disease (Sotaniemi, Ylöstalo and Kauppila, 1974). This is especially true for patients in an intensive-care unit, with respiratory failure as a result of severe trauma, tetanus or postoperative complications following major thoracic or abdominal surgery. During the period of respiratory support they receive a variety of drugs (Sotaniemi and Palva, 1972; Rietbrock and Richter, 1978).

How the body handles such drugs during severe illness is not understood clearly. Changes in total liver cell mass, liver blood flow and individual liver cell function, including the activity of the drug-metabolizing enzyme systems are important, and modify the disposition of multiple drug therapy on liver function in these patients. Among the conventional liver function tests only the γ-glutamyltranspeptidase (γ-GT) activity increases in proportion to the duration of drug treatment (Rietbrock and Richter, 1978). Furthermore, in such patients, even in the absence of cardiac disease, the size of the liver increases rapidly by an average of almost 100% during the 1st week of treatment (Rietbrock and Lazarus, 1979). This enlargement of the liver is a genuine hypertrophy and reflects mainly an increase in cytoplasmic volume. The meaning of the alterations in serum γ-GT and liver growth are open to various interpretations (Schmidt and Schmidt, 1973; Whitfield et al., 1973; Davidson, McIntosh and Ford, 1974; Goldberg and Martin, 1975; Hildebrandt et al., 1975; Rietbrock and Lazarus, 1979).

The purpose of the present investigation in patients with respiratory disturbances and in an intensive care unit was to study the effects of the multiple administrations of drugs on the pharmacokinetics of hexobarbitone at different times during the period of artificial ventilation. Hexobarbitone is completely metabolized in the liver by microsomal enzymes and was chosen, therefore, as a model substance. Its pharmacokinetics are not influenced by protein binding and it is used widely as an indicator of changes in drug metabolizing activity (Bush and Weller, 1972). It can be used therapeutically in patients during mechanical ventilation to maintain sedation. Numerous reports are available about the changes of hexobarbi-

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CEREBRAL PROTECTION BY BRAIN RETRACTION PRESSURE MONITORING

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Cerebral hypoxia and ischaemia with resulting tissue damage can occur during intracranial procedures because of prolonged or high pressures, or both, generated by the retractor blade on brain (Albin et al., 1977).

During the past 5 years we have developed instrumentation to quantitate the amount of brain retraction pressure (BRP) induced on brain and the various thresholds necessary to produce physiopathological changes. Currently, the retractors are fitted within a pressure-sensitive sleeve and placed on brain, allowing for the continuous monitoring of BRP.

In our animal experiments we have noted that the pressure threshold for the development of histological changes after 1 h of retraction at normotensive arterial pressure was greater than 20 mm Hg and at induced hypotensive arterial pressure was reduced to 10 mm Hg. We have also shown the correlation of somatosensory cortically evoked responses (SER) to the development of lesions and to cerebral perfusion pressure (CPP), with greater CPP showing a smaller decrease in SER and greater resistance to histopathological changes (Bennett et al., 1977; Albin et al., 1980). During ipsilateral somatosensory cortex BRP at 20 mmHg for 1 h we have also detailed a concomitant contralateral distribution of this focal pressure as monitored by an increase in cisterna magna pressure. Our experimental studies have also indicated a decrease in mean hemispheric and cortical blood flow in retracted and contralateral areas, which was considerably greater under induced hypotension than under normotension, and loss of autoregulation in the hypotensive group (Bennett et al., 1977).

We have now monitored BRP in more than 50 patients where both hand-held and mechanically fixed brain retractors were used. A transitory BRP to 125 mm Hg has been noted in one case of hand-held retraction, and in five of 10 intracranial aneurysms carried out under induced hypotension, the BRP came close to or momentarily exceeded the CPP.

The continuous monitoring of BRP and the use of the SER as an indication of adequacy of cerebral perfusion can be helpful in protecting the brain from iatrogenic pathology.

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CORTICAL $P_{t\mathrm{CO_2}}$ DURING AND AFTER MIDDLE CEREBRAL ARTERY OCCLUSION

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Occlusion of the circulation to the brain rapidly depletes oxygen stores and stimulates glycolysis. With lactic acid liberation of carbon dioxide from HCO_3, the partial pressure of carbon dioxide will increase rapidly. Case, Felix and Castellana (1980) have reported $P_{t\mathrm{CO_2}}$ measurements in excess of 53.2 kPa after 17 min of myocardial ischaemia. Such high concentrations of carbon dioxide might lead to supersaturation and bubble formation contributing to irreversibility by increasing tissue pressure and blocking capillaries. We attempted to determine if a similar increase in $P_{t\mathrm{CO_2}}$ occurs in cerebral cortex following middle cerebral artery occlusion (MCAO). Five cats were anaesthetized with halothane–nitrous oxide 0.8%/70%, paralysed and mechanically ventilated. Four 25-μm, Teflon-coated platinum wires were inserted into the cortex for local cortical blood flow (l.c.b.f.) measurements by hydrogen clearance. A surface $P_{t\mathrm{CO_2}}$ electrode with temperature controlled at 37 °C was placed over the Pt electrodes on the suprasylvian gyrus in a location where previous experiments with oxygen availability and hydrogen flow determinations had shown rapid oxygen depletion and maximal flow reductions (Ingvar et al., 1979) Control cortical $P_{t\mathrm{CO_2}}$ was 4.99 ± 0.62 kPa while arterial $P\mathrm{CO_2}$ was 3.96 ± 0.53 kPa. $P_{t\mathrm{CO_2}}$ following MCAO was found to increase within 2 min and increase at a rate of 2.21 ± 0.89 kPa $\mathrm{min^{-1}}$. This is similar to the responses measured in heart ($= 2.21$ kPa $\mathrm{min^{-1}}$). Cortical $P_{t\mathrm{CO_2}}$ was 11.89 ± 2.37 kPa at 8 min after MCAO. A second phase during which $P_{t\mathrm{CO_2}}$ increased at a slower rate of 0.33 ± 0.24 kPa $\mathrm{min^{-1}}$ followed the initial rapid increase. l.c.b.f. was reduced from 111.1 ± 67.5 ml $\mathrm{min^{-1}}$/100 g to zero with MCAO. In previous experiments, in such electrodes oxygen availability decreased to near zero within 30 s. In two animals, when MCAO was released within 10 min, $P_{t\mathrm{CO_2}}$ decreased to 4.00 ± 0.31 kPa (arterial $P\mathrm{CO_2} = 3.56 \pm 0.28$ kPa) reflecting a post-occlusion hyperaemia (c.b.f. $= 311 \pm 134$ ml $\mathrm{min^{-1}}$/100 g), and then returned to normal (4.75 ± 0.86 kPa) over a 30-min period as c.b.f. decreased to control values (134.7 ± 77.9 ml $\mathrm{min^{-1}}$/100 g). The increase in $P_{t\mathrm{CO_2}}$ was undiminished in a second MCAO when MCAO was maintained for less than 10 min. A subsequent MCAO with pentobarbitone replacing the halothane resulted in a slower increase in $P_{t\mathrm{CO_2}}$ in one animal with no difference in rate of increase in a second. In both animals $P_{t\mathrm{CO_2}}$ reached at 5 min was less than the previous MCAO with halothane anaesthesia. In all animals $P_{t\mathrm{CO_2}}$ reached a plateau at 14.50 ± 5.05 kPa, but after sacrifice by injection of potassium chloride i.v., $P_{t\mathrm{CO_2}}$ increased further at 0.27 ± 0.20 kPa $\mathrm{min^{-1}}$. At $P_{t\mathrm{CO_2}}$ 14.50 kPa, intracellular pH will have decreased by about 0.45 units. Thus, acidosis develops at a rapid rate initially but the increase in $P_{t\mathrm{CO_2}}$ appears to be limited by its diffusion to adjacent perfused tissue. $P_{t\mathrm{CO_2}}$ of the cortex may provide a more sensitive measure of the volume of ischaemic tissue than oxygen availability.

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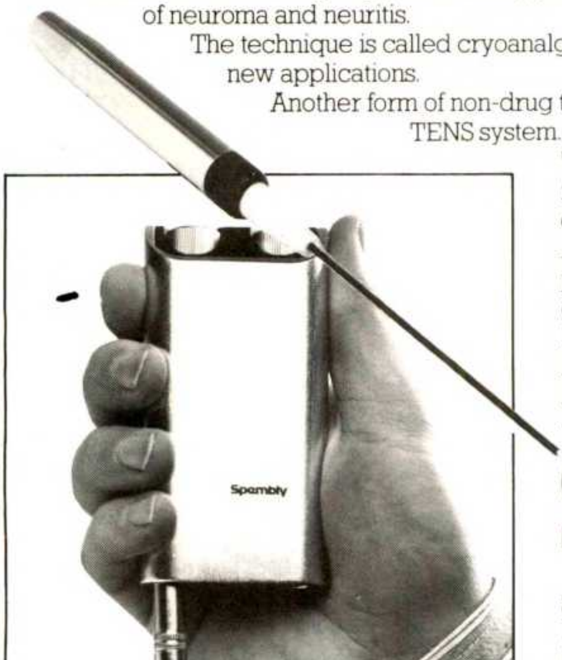

This study confirmed that the optimal site to block the intercostal nerves is at the angle of the rib, not only because the groove in the rib is broadest and deepest at this point, but because the fat which accumulates in the thoracic cage of a well-nourished patient lies over the ribs and anterior to its groove in this area. Therefore, it provides additional protection against pleural puncture (fig. 2A).

ACKNOWLEDGEMENTS

The author acknowledges with appreciation the assistance and co-operation of D. Bauermeister, S. P. Hammar, R. F. Wheelis, S. Patterson and D. Dail, staff physicians of the Department of Pathology of The Mason Clinic and the Virginia Mason Hospital, their two dieners, Harry M. Anderson and James W. Gordon, as well as R. Sundberg, T. Ubben and R. Schlag of the Department of Medical Photography.

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BLOCAGE DU NERF INTERCOSTAL: DISSEMINATION DE L'ENCRE DE CHINE INJECTEE DANS L'ESPACE INTERCOSTAL

RESUME

On a injecté bilatéralement dans l'espace intercostal situé entre la 9è et la 10è côte de 14 cadavres, 3 et 5 ml d'encre de Chine. La dissémination de l'encre a été observée, puis on a disséqué l'espace intercostal se trouvant entre les côtes où l'on avait fait l'injection, de même que celui immediatement au-dessus et celui immédiatement au dessous L'étude de Nunn et Slavin (1980) d'injections similaires sur deux cadavres fait ressortir qu'une injection dans un espace intercostal bloquait non seulement le nerf intercostal de cet espace, mais aussi au moins celui immédiatement au-dessus et celui immédiatement au-dessous. Cette étude a permis de vérifier le rapport établi précédemment par l'auteur à savoir que le nerf intercostal se trouvant dans l'espace intercostal injecté est le seul qui soit anesthésié.

INTERCOSTAL-NERVENBLOCKIERUNG. AUSBREITUNG VON TUSCHE, DIE DIE IN DIE RIPPENRILLE INJEZIERT WURDE

ZUSAMMENFASSUNG

Drei und funf Milliliter Tusche wurden bilateral in die Rippenrillen der 9. und 10. Rippe von 14 Kadavern eingespritzt. Die Ausbreitung der Tusche wurde beobachtet, und die Rille der injezierten Rippen wurden seziert, ebenso wie die darüber und die darunter. Eine von Nunn und Slavin durchgefuhrte Studie (1980) ähnlicher Injektionen in zwei kadaver zeigte, dass durch die Injektion einer Rippenrille nicht nur der Intercostalnerv dieser Rille, sondern auch der der daruber und der darunterliegenden Rille blockiert wurde. Die jetzige Studie bestätigte den fruheren Bericht des Autors, demzufolge nur der Intercostalnerv in der Costalrille der injezierten Rippe anasthesiert wird.

BLOQUEO DEL NERVIO INTERCOSTAL: DISPERSIÓN DE LA TINTA CHINA INYECTADA A LA FISURA COSTAL DE LA COSTILLA

SUMARIO

Se inyectaron bilateralmente tres y cinco mililitros de tinta china en la fisura costal de la novena y décima costillas de 14 cadáveres Se observó la dispersión y se seccionó la fisura costal de la costilla inyectada, junto con la inmediata inferior y la inmediata superior. El estudio de Nunn y de Slavin en 1980 sobre inyecciones similares en dos cadáveres indicó que una inyección en una fisura costal bloqueó no sólo el nervio intercostal de esa fisura, sino también por lo menos el de la inmediata superior y el de la inmediata inferior. El presente estudio verificó el informe previo del autor en el que se declara que sólo se anestesia el nervio intercostal de la fisura costal perteneciente a la costilla inyectada.

Br. J. Anaesth. (1981), 53, 351

NON-INVASIVE MEASUREMENT OF CARDIAC OUTPUT DURING ANAESTHESIA

An evaluation of the soluble gas uptake method

C. P. H. HENEGHAN AND M. A. BRANTHWAITE

SUMMARY

A technique for measuring cardiac output which depends on the uptake of an inert soluble gas from the lungs has been evaluated during anaesthesia. A respiratory mass spectrometer has been used to follow the concentrations of argon and freon-22 during passive rebreathing in anaesthetized patients before cardiopulmonary bypass. Values for cardiac output obtained with this technique are reproducible, but lower than those recorded using the direct Fick technique before and after the rebreathing manoeuvre A reduction in cardiac output caused by vigorous rebreathing is the most likely explanation for the discrepancy and, although serial measurements of oxygen consumption may permit application of a correction factor, a method of measurement which causes significant haemodynamic disturbance cannot be recommended for widespread use.

Methods for measuring cardiac output which depend upon the uptake of an inhaled, soluble gas have been reported by a number of authors (Cander and Forster, 1959; Cerretelli et al., 1966; Teichmann et al., 1974; Sackner et al., 1975; Peterson et al., 1978; Petrini, Peterson and Hyde, 1978; Severinghaus, Ozanne and Louderbrough, 1978; Denison, Davies and Brown, 1980); multiple breath hold, rebreathing and single breath techniques have been described. A figure for accessible, or effective pulmonary blood flow rather than cardiac output is obtained unless the test gas reaches all perfused alveoli and, even if this requirement is fulfilled, the result will not reflect cardiac output immediately before or after the manoeuvre if the measurement technique itself causes an abrupt haemodynamic change.

The extent to which these factors limit the value of the method as a means of measuring cardiac output during anaesthesia and controlled ventilation has been explored by a comparison with the direct Fick technique.

PATIENTS AND METHODS

Seven adult patients were studied during elective open heart surgery; clinical details are given in table I. All measurements were made after median sternotomy, but before cannulation of the heart. The lungs were being ventilated with a nitrous oxide–oxygen mixture and each patient had received a paralysing dose of pancuronium bromide with either papaveretum or fentanyl.

Inert soluble gas technique

The patient was disconnected from the anaesthetic circuit and allowed to exhale passively to functional residual capacity through a Haldane tap open to the atmosphere. The tap was then turned to a rebreathing bag containing either 1 or 2 litre of a mixture of 3.5% freon-22, 10% argon, 35% oxygen and 51.5% nitrogen, and the lungs were ventilated with this mixture by manual compression of the bag six or seven times in approximately 15–20 s. The concentrations of argon and freon were recorded throughout the manoeuvre using a Centronic MGA 200 mass spectrometer with anaesthetic correction circuits (Davis and Spence, 1979), and sampling through a fine catheter introduced into the suction cap on the endotracheal tube connector. A digitizer and Prime 300 computer were used to calculate pulmonary blood flow (Salt, Gothard and Branthwaite, 1980).

Direct Fick technique

A series of at least six measurements of oxygen consumption was made using the same mass spectrometer, a mixing box and two tracer gases (Heneghan, Gillbe and Branthwaite, 1981). During each series, heparinized blood samples were

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SUBARACHNOID ANAESTHESIA WITH BUPIVACAINE FOR ORTHOPAEDIC PROCEDURES IN THE ELDERLY

P. J. NIGHTINGALE AND T. MARSTRAND

SUMMARY

The use of a plain 0.5% solution of isobaric bupivacaine for spinal anaesthesia is described in a consecutive series of 410 patients undergoing orthopaedic operations on the lower limbs. It gave analgesia of sufficient extent, duration and degree in 96.6% of cases for procedures that lasted up to 250 min. The most common problem was arterial hypotension which required sympathomimetic therapy in 37.7% of patients.

The use of bupivacaine for subarachnoid (spinal) anaesthesia was first reported by Ekblom and Widman (1966) and it has been used successfully for lower abdominal and lower limb surgery in concentrations of 0.5%, 0.75% and 1%, both with and without adrenaline (Hengesbach and Matthes, 1977; Nolte et al., 1977; Lanz, Schellenberg and Theiss, 1979; Stratmann et al., 1979). It has a long duration of action (Ocker, 1966; Roy, Multani and Lala, 1975) although no longer than that of amethocaine in spinal anaesthesia (Pflug, Aasheim and Beck, 1976; Lanz, Schellenberg and Theiss, 1979). Unlike amethocaine, it withstands repeated autoclaving (Watt, Ross and Atkinson, 1968; Martindale, 1977). Previous studies have included patients of all ages, but the suitability of intrathecal bupivacaine has not been investigated specifically in the elderly. This prompted us to undertake a trial of 0.5% plain isobaric bupivacaine in such patients undergoing orthopaedic procedures.

METHODS

Patients over the age of 60 yr who were to undergo orthopaedic operations for the treatment of fractures of the lower limbs in the Surgical Unit of Sundby Hospital, Copenhagen, were studied. Lumbar sepsis, recent head or spinal injury, possible intracranial hypertension, previous lumbar surgery and a bleeding tendency or anticoagulant therapy were considered absolute contraindications to use of the technique.

Immediately before lumbar puncture pentazocine 0–90 mg (mean 32 mg) and diazepam 0–20 mg (mean 6 mg) were injected i.v. until the patient was lightly sedated. The patient was then placed in the lateral position, with the fracture site uppermost, and a standard mid-line lumbar puncture performed at the 3rd or 4th interspace with a 22-gauge needle. On obtaining clear spinal fluid 3–4 ml of 0.5% plain bupivacaine (Marcain, Bofors Nobel–Pharma, Sweden) was injected over 30 s with barbotage. The mean dose was 16.7 mg. Once the fracture site was free of pain the patient was placed supine. The operating table was horizontal throughout.

The time at which the fracture became analgesic was recorded and then the upper level of analgesia to pin-prick was noted during onset and regression of blockade. Arterial pressure (sphygmomanometer) and heart and respiratory rates were monitored during the anaesthetic procedure, the operation itself and in the recovery room after operation. Hypotension was treated with i.v. fluids and head-down tilt, plus i.m. or i.v. ephedrine if these measures did not prevent a decrease in arterial pressure of approximately 25%. When the clinical condition permitted, and with the return of active toe movements, the patients were returned to the surgical ward where they were kept supine for 24 h.

RESULTS

Patients in whom lumbar puncture was unsuccessful were excluded from the series, leaving 410 consecutive patients (40.3% male), ranging in age between 60 and 94 (mean 76.7) yr, in the study. All were in ASA categories I–III. Seventy-seven per

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CONTROL OF POSTOPERATIVE PAIN BY INTERACTIVE DEMAND ANALGESIA

C. J. HULL AND A. SIBBALD

SUMMARY

A demand analgesia apparatus is described. It communicates with the patient by means of spoken messages in any desired language, so that preliminary instruction is unnecessary. Dosage is limited by a reduction in respiratory rate, and by a series of electronic fail-safe circuits. Operation of the system is illustrated in a series of 10 patients given fentanyl "on demand" for the first 12 h after operation. The mean dose rate 0.73 ± 0.49 µg min^{-1}. There was no evidence of cumulation or tolerance during the period of study.

In the early period after operation a "standard" dose of an opiate given i.m. is frequently found to be either excessive or ineffective (Stapleton, Austin and Mather, 1978).

An alternative approach is to give small doses of opiate i.v. *when the patient decides* they are necessary. Early attempts to introduce this concept to clinical practice (Sechzer, 1968, 1971; Forrest, Smethurst and Kienitz, 1970; Scott, 1970; Keeri-Szanto, 1971; Keeri-Szanto and Heaman, 1972) showed that satisfactory pain relief could be achieved in a large proportion of cases, with a high degree of patient acceptance. However, the success of the technique depends upon the choice of apparatus. These early studies used simple devices with few refinements, so that close supervision was necessary and patients required a clear understanding of the method.

The "Cardiff Palliator" is more sophisticated (Evans et al., 1976), having a number of fail-safe systems. The patient is required to press a "call" button when in pain, whereupon a motorized syringe delivers a preset dose of drug. Each successful demand is accompanied by an audible "bleep" from the apparatus. After administration of a demand dose of drug, the system remains refractory to further demands for a presettable period (up to 99 min). Rosen (1977) has shown that the method can be effective, but the design has some limitations. First, a drowsy patient recovering from major surgery cannot be relied upon to remember what is required of him, so that he may not activate the device unless preoperative instruction is reinforced by a nurse or doctor. Second, a refractory period may lessen the patient's confidence; he may fear that the machine has broken down. Pre-operative instruction may heighten anticipation of pain and may increase anxiety. In any case, the short-term amnesia which often follows major surgery may render instruction ineffective.

A system of interactive demand analgesia has been developed, which requires no pre-operative instruction and permits dosage whenever desired (Hull, Sibbald and Johnson, 1979). Whilst designed to deliver fentanyl, the apparatus can be used with any rapidly acting analgesic suitable for i.v. administration.

The method is based upon conversational interaction between apparatus and patient; the apparatus "talks" to the patient in English (or any other language) and the patient signals to the apparatus with a press-button. Since the machine's instructions are self-explanatory, no instruction or reinforcement by staff is necessary. The spoken messages are intended to give the patient constant reassurance that pain relief is available when required, so that overdosage induced by anxiety is unlikely to occur. Confidence in any method of analgesia is all important. Not only must it be effective,—the patient must believe that it is.

It can be postulated that the patient is likely to become conditioned to associate the cue ("if you are in pain...."), and a positive response (two presses) with analgesia. Therefore it follows that the patient may obtain a degree of relief from the cue–response process itself, thus minimizing the requirements for active drug.

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(normally 8 s), the apparatus ceases to give maintenance doses and will refuse to initiate a new cycle until the interval has remained below the threshold for 1 min.

A front panel display informs the clinician as to the elapsed time since switch-on, the total dose given, the maintenence dose, the status of the pneumograph monitor, and the current position in the operational cycle.

The only adjustment accessible to the clinician is the incremental dose, which he can set within the range 1–29 µg of fentanyl. The cassette tape bearing the message is "posted" into the replay unit before the system is switched on, so that it is possible to select the preferred language (and sex) for the patient concerned. If desired, the tape can be exchanged for another at any time.

PRINCIPLE OF OPERATION (fig. 2)

The tape replay system, dosage pump, fail-safe devices and displays are all directly controlled by a central logic system.

The d.c. supply to the auto-reverse stereo tape replay unit is controlled electronically so that it can be activated by the central logic system. The tape is organized so that track A carries both messages in sequence, separated by a 15-s pause, repeated throughout the track (fig. 3). Track B contains two signalling tones. The first tone (1314 Hz) is placed immediately before and the second (615 Hz) immediately after the second message. The "reversed" tracks are similarly recorded, so that the cassette forms a 60-min tape loop. Signals from track B are led to tone detection circuits, enabling the central logic system to synchronize the tape motor precisely. Signals from track A pass through a voltage-controlled attenuator before connection with the patient's earphone, so that the logic system can allow the patient to hear the second message, or not, according to requirement.

The sequence operates as follows. On receipt of a "clock" or "call" signal, the OR gate initiates a new cycle. This can only occur if the AND gate is not inhibited by the respiratory monitor or the "minimum period" (which ensures that 1 min elapses between cycles). If the AND gate passes the signal, the tape motor is switched on, the audio channel enabled, and the patient hears the first message followed by 15 s silence. In order to receive a dose of drug he must press the button twice during this period. When the 1314 Hz tone is detected, a data register containing the "number of presses" is interrogated. A count of two allows the audio channel to remain open, the dose is given, and the tape runs until the second tone is detected, whereupon the tape motor is turned off and the audio channel closes. A zero count mutes the audio channel so that the patient does not hear the

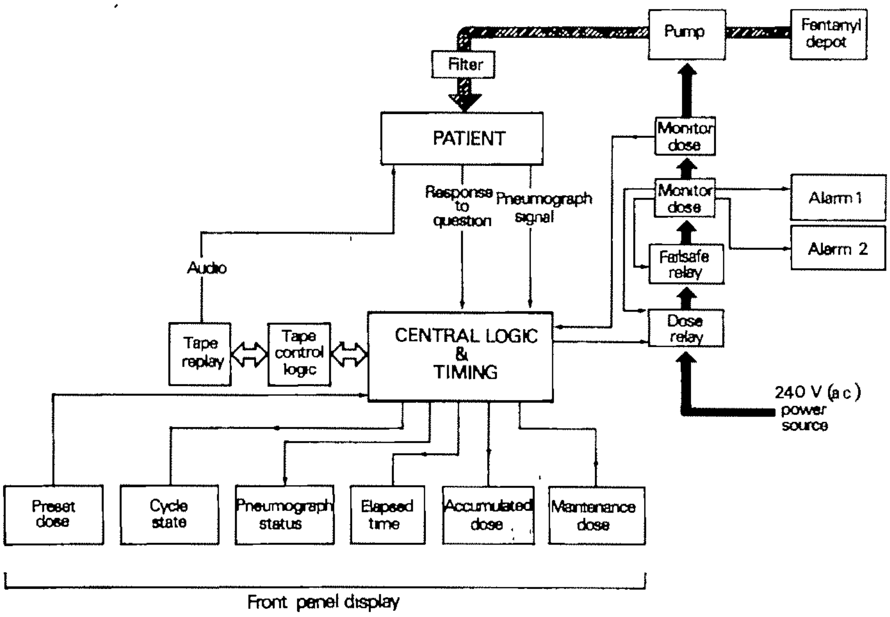
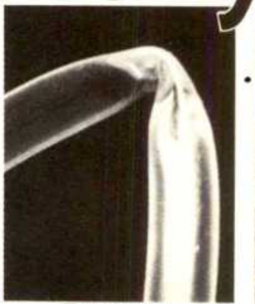


FIG. 2. Functional diagram. The patient is an integral part of a closed-loop control system.

IV therapy can be it's own worst enemy

Empty container

Occlusion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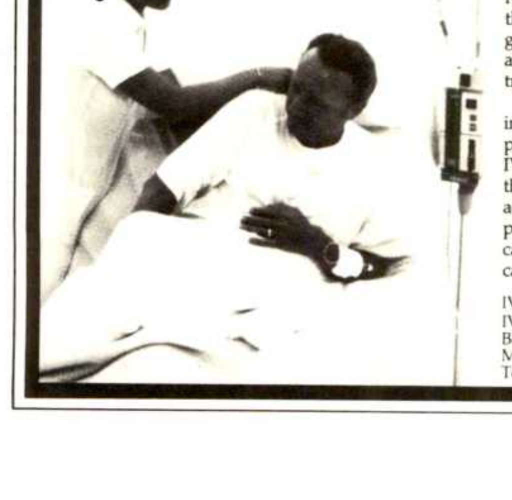

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VOLUME 53, No. 5 MAY 1981

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EDITORIAL

ANTICHOLINERGIC PREMEDICATION AND REGURGITATION

The use of anticholinergic drugs for premedication in adults is controversial. Over the past decade, their use has declined considerably, although in a recent survey it was found that 62% of anaesthetists in Great Britain still routinely prescribed these drugs (Mirakhur et al., 1978), mainly for the stated purpose of reducing secretions, both salivary and bronchial. Although anticholinergic actions were formerly of great importance, particularly when diethyl ether enjoyed a vogue, the use of non-irritant volatile anaesthetic agents, and a smooth unhurried approach to induction of anaesthesia minimize problems induced by excessive secretomotor activity. Moreover, it is well recognized that the dry mouth and paralysis of ocular accommodation produced by atropine are very unpleasant for the patient.

Another claimed advantage for anticholinergic premedication is the protection this affords against vagal overactivity, although the predominant responses of laryngoscopy, intubation and surgery are sympathetic in origin rather than parasympathetic (Prys-Roberts et al., 1971). Hyoscine has been promoted for both its antiemetic and amnesic properties, although there are more specific and effective drugs available for both purposes. A marked disadvantage is that it may produce restlessness, especially in elderly patients.

There is, however, one situation in which there is a good indication for the use of anticholinergic drugs before endotracheal intubation: where repeated doses of suxamethonium are used. In the 1973–75 Confidential Enquiry into Maternal Deaths there were two deaths attributed to "misuse of drugs". In both patients atropine was avoided, although in one instance tacrine was administered in combination with suxamethonium, and in the second the relaxant was used in repeated doses. Both patients developed bradycardia which progressed to cardiac arrest.

The major anaesthesia-related cause of maternal deaths has consistently been pulmonary aspiration consequent upon vomiting or regurgitation. This has stimulated interest among anaesthetists in a structure termed the lower oesophageal sphincter. This is an area at the lower end of the oesophagus which is maintained at a higher resting pressure than the intragastric pressure. Although it cannot be defined anatomically, simple manometry allows a description of its length and tone and it is generally agreed that the sphincter plays a major role in preventing gastro–oesophageal reflux (Cohen and Harris, 1971). Other mechanisms including the gastro–oesophageal angle, the oesophago–phrenic ligament and the crura of the diaphragm are now thought to play minor roles in preventing gastro–oesophageal reflux. It is important to appreciate that it is not the tone of the LOS itself which prevents reflux, but the pressure difference between the stomach and the oesophagus; this is termed the barrier pressure.

There is enormous variation in barrier pressures in normal individuals. Although a correlation between gastro–oesophageal reflux and decreased barrier pressure has been reported (Haddad, 1970), there is considerable overlap between barrier pressures of normal subjects and those of patients with reflux. It is not possible, therefore, to define a threshold of barrier pressure below which reflux would occur in an individual patient. The diagnosis of an incompetent sphincter can be made only by using a pH electrode in the oesophagus to monitor reflux of dilute acid placed in the stomach and not by pressure manometry of the lower

20, 42 and 43 (Webb and Weaver, 1979b) were calculated (table III).

Of the non-muscle tissues only liver and blood had significant regression coefficients, whilst all muscles, with the exception of triceps had significant regression coefficients.

Both regression coefficients were found to be positive and significant and the log transform regression on muscle density is presented in table IV.

DISCUSSION

If the 95% confidence limits of the horse population are expressed as percentages of the mean (table II) and compared with those for dog (Steward, Allott and Mapleson, 1975) and for rabbit (Mapleson, Allott and Steward, 1972) it can be seen that, with the exception of brain, myocardium and extensor carpi radialis muscle, the confidence limits for the horse's tissue/gas partition coefficients are larger. These differences most probably reflect the heterogenous nature of the horse sample in comparison to the more homogenous rabbit strain (New Zealand White) and the large breed bias of the dog sample (two-thirds were Alsatians). It would be interesting to look at data for more diverse sample populations of other species to see whether the horse is special in having its partition coefficients so affected by factors such as body condition, type, age and sex.

The comparison of the spleens from postmortem room and knackery showed a wider variance between spleens from the postmortem room, which may have resulted from the varied degree of

between-horses residual mean square (RMS) has a highly significant variance ratio (VR) with respect to the within-horses mean square *P *<0.05;* **P *<0.01;* ***P *<0.001. § Mean square between levels of factor*

with factorization†

Origin				
RMS	d.f.	MS§	d.f.	VR‡
0.0030	29	0.0017	1	0.57
0.0042	17	0.0187	1	4.46*
0.0106	36	0.0047	1	0.44
0.0043	33	0.0024	1	0.56
0.0793	36	0.6863	1	8.65*
0.0214	36	0.0549	1	2.57
0.1297	34	0.2377	1	1.83
0.0068	33	0.000002	1	0.000
0.0076	33	0.0563	1	7.40*

Condition combination factors

Condition × Sex					Condition × Type				
RMS	d.f.	MS§	d.f.	VR‡	RMS	d.f	MS§	d.f.	VR‡
0.0711	32	0.2532	5	3.56*	0.0699	34	0.3881	3	5.55**
0.0144	12	0.2194	5	15.21***	0.0195	14	0.3321	3	17 00***
0 0366	16	0.0686	5	1.87	0.0228	18	0.1725	3	7.56**
0.0123	15	0.0238	5	1.94	0.0101	17	0.0437	3	4.31*
0 0642	16	0.2014	5	3.14*	0.0541	18	0 3535	3	6.54*
0.1014	15	0.3185	5	3.14*	0.0833	17	0.5658	3	6.80**
0.0151	15	0.1088	5	7.19**	0.0234	17	0.1243	3	5.30**
0.0319	17	0.1065	5	3.34*	0.0298	19	0.1692	3	5.68**
0.0119	15	0.1558	5	13.08***	0.0096	17	0.2650	3	27.67***

IV therapy can be it's own worst enemy

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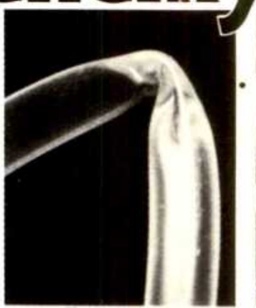
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VOLUME 53, No. 6 JUNE 1981

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EDITORIAL

TOXICITY CAUSED BY LOCAL ANAESTHETIC DRUGS

Systemic toxicity from local anaesthetic drugs is a rare but unpleasant complication of regional anaesthesia when moderate to high dosage is used. In the main it occurs when the injection is made accidentally into a blood vessel. Signs and symptoms such as numbness of the tongue, light-headedness, visual disturbance and muscular twitching give warning of the more serious events which may follow, namely convulsions, coma, respiratory arrest and cardiovascular depression.

There is good evidence that, with drugs such as lignocaine, there is a wide margin between central nervous system toxicity and cardiovascular depression. Indeed, because the former causes apnoea, cardiovascular depression is often secondary to hypoxia rather than a primary effect of the drug. The minimum lethal dose of lignocaine in dogs may be increased four-fold if the lungs are ventilated rather than allowed to remain apnoeic (Woods and Haggart, 1957).

Recently this separation of central nervous system and cardiovascular toxicity has been questioned in regard to the longer acting drugs bupivacaine and etidocaine (Albright, 1979). Case reports have appeared suggesting that severe cardiac depression, often leading to cardiac arrest, may occur soon after the appearance of convulsions. Experimentally, cats have been shown to suffer from cardiac arrhythmia during the infusion of bupivacaine (de Jong and DeRosa, 1981), an odd reaction in view of the anti-arrhythmic activity of local anaesthetics and one which does not appear to occur in dogs (Jorfeldt et al., 1968) and, perhaps more pertinently, in primates (Munson, Paul and Embro, 1977).

Before accepting that cardiovascular depression is a direct effect of the injected drug, other factors must be considered. It is not sufficiently realized how quickly hypoxia can occur in a convulsing patient. During a grand mal attack effective ventilation ceases and oxygen is used at a very fast rate, certainly many times that of the resting subject. While there is little evidence of a significant increase in cerebral oxygen consumption during convulsions, cerebral and myocardial oxygen supply will deteriorate rapidly as the contracting muscles use up the meagre oxygen reserves. This highlights the urgent necessity of stopping convulsions and giving oxygen, the two most important procedures in treating toxicity. The rapidity with which hypoxia and acidosis may occur has been illustrated recently (Moore, Crawford and Scurlock, 1980), and central nervous system toxicity from local anaesthetics is greatly enhanced by acidosis and hypercapnia (Engelsson and Matousek, 1975).

The treatment of convulsions has been an item of controversy for some years. Classically, thiopentone was the agent of choice and there is little doubt of its ability to stop convulsions quickly in moderate doses (150–300 mg). More recently, diazepam has achieved popularity as it has been shown in animals to be effective in both prevention and treatment of local anaesthetic-induced convulsions (de Jong, 1978). However, its stated advantages over thiopentone in regard to cardiovascular depression ignore two important points. First, it is much slower in effect, taking as long as 2–3 min to control convulsions (Moore, Balfour and Fitzgibbons, 1979), therefore making assess-

(Nunn, 1980). The reduction in cardiac output in the anaesthetized groups may be associated with an increase in the transit time through the lungs, so that the injected propranolol would be exposed to pulmonary endothelium for a longer period. Since uptake of the drug is thought to occur in endothelial cells (Junod, 1975), the increased duration of exposure should result in increased uptake. However, change in cardiac output is unlikely to be the only explanation since no correlation was found between propranolol uptake and cardiac output in conscious dogs (Pang et al., 1980), although the range of cardiac output was less in anaesthetized animals used in this study. Also, concentration of propranolol by isolated rat lungs was enhanced by lignocaine even when conditions of perfusion were identical (Dollery and Junod, 1976). Finally, Street and others (1979) found increased tissue concentrations of propranolol in lung and brain when the drug was administered i.v. under halothane and nitrous oxide anaesthesia. It is attractive to postulate a common mechanism of uptake in both organs.

The accumulation of propranolol in the lung may be caused by its high lipid solubility. This is supported by a positive correlation between the degree of lung uptake and the log partition coefficient of β-adrenoceptor antagonists between octanol and buffer (Street et al., 1978). This affinity for lipids may be an important factor in explaining our results. All the anaesthetic agents which have been associated with an increase in propranolol uptake—lignocaine, thiopentone, nitrous oxide and halothane—are themselves highly lipid-soluble. Therefore, it is possible they may interact with the endothelial cell membrane and facilitate uptake of the drug. If this hypothesis is true, it may explain why propranolol uptake in the brain also is enhanced by anaesthetic agents. Moreover, the difference observed between groups B and C in our experiments may be related to the absence of halothane, which is more lipid-soluble than nitrous oxide. Alternatively, it is possible that fentanyl may affect the uptake process.

Increased propranolol uptake by the lungs of animals under general anaesthesia will be associated with a smaller arterial concentration after i.v. administration of the drug. After withdrawal of anaesthetic, the pattern of release of previously accumulated drug into the systemic circulation is unknown. In man, oral administration of propranolol is associated with reduced lung uptake of an i.v. dose of the drug (Geddes et al., 1979). These considerations may be of therapeutic relevance in anaesthetic practice and the lungs should not be overlooked as a potential site for drug interaction.

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FIXATION DE PROPRANOLOL ACCRUE APRES UN PREMIER PASSAGE DANS LES POUMONS DE CHIENS ANESTHESIES

RESUME

On a étudié sur trois groupes de chiens Labrador la fixation du ^{14}C-propranolol, après un seul passage dans la circulation pulmonaire en utilisant une méthode de dilution à double indicateur. Le fixation sur les animaux conscients et capables de se déplacer a été de 53%. Elle est passée à 81% sur les chiens anesthésiés au thiopentone, protoxyde d'azote et halothane, et à

RESULTS

The mean preanaesthetic QT intervals (±SD) ranged from 425±39 to 447±37 ms in different groups.

There was no disturbance in the e.c.g. 1 min before venepuncture. Table II shows that junctional rhythm occurred in 4–16% of the children in the adenoidectomy groups. In the T+A groups, the frequency of junctional rhythm ranged from 11% to 33%. The frequency of upper and middle junctional rhythms was similar in each group.

TABLE II. *Frequency (%) of e.c.g. changes during inhalation anaesthesia with controlled ventilation in different groups. Number of children in parentheses. BBB = bundle branch block.* *$P < 0.05$; **$P < 0.01$ *from the corresponding halothane groups*

	Junctional rhythm		QRS complex changes		
	Upper	Middle	BBB	BBB + aberrant conduction	Biphasic T-wave
Halothane					
Adenoidectomy					
Thiopentone (20)	5	5	0	10	0
Althesin (25)	16	16	4	4	8
T+A					
Thiopentone (27)	30	33	4	11	0
Enflurane					
Adenoidectomy					
Thiopentone (25)	12	12	0	0	32**
Althesin (27)	4	7	0	0	41**
T+A					
Thiopentone (27)	11	15	0	0	15*

Neither bundle branch block (BBB) nor BBB plus aberrant conduction was seen during enflurane anaesthesia, whereas the frequency of BBB ranged from 0% to 4% and BBB plus aberrant conduction was seen in six children in the halothane groups. Aberrant conduction was always associated with the surgical manipulation. In addition to the results shown in table II, one child in the Althesin plus halothane group developed BBB with aberrant conduction before the start of spontaneous breathing when the end-tidal carbon dioxide was 9.5%, but this disappeared after breathing 100% oxygen. In three children BBB and aberrant conduction disappeared without treatment. In the remaining three children, e.c.g. became chaotic and this lasted more than 5 min. Administration of lignocaine 1 mg kg^{-1} i.v. promptly abolished the arrhythmia. The mean duration (±SEM) of QT interval during BBB with aberrant conduction was 477±14 ms. In the children treated with lignocaine the mean pretreatment (±SEM) QT interval was 509±24 ms and decreased significantly after lignocaine, followed by sinus rhythm (437±9.7 ms) ($P<0.05$).

The T wave became biphasic in 15–41% of the children anaesthetized with enflurane and in 0–8% anaesthetized with halothane. A typical example of T wave becoming biphasic is shown in figure 1. The arterial pressure was maintained during all types of e.c.g. changes.

Figure 2 shows that the mean preanaesthetic QT interval was significantly longer (492±22 ms) in the children showing BBB plus aberrant conduction than in the children without e.c.g. changes (426±5.2 ms) ($P<0.01$) and in the children with junctional rhythm or BBB (438±5.3 ms) ($P<0.05$). Figure 3 shows the e.c.g. changes of a healthy 9-yr-old boy undergoing T+A with halothane anaesthesia. Preanaesthetic QT interval was 594 ms. During the dissection of the left tonsil there was aberrant conduction with chaotic rhythm which resulted in bifocal ventricular tachycardia. A regular supraventricular rhythm was restored after injection of lignocaine 1 mg kg^{-1} i.v. and sinus rhythm followed. This boy's QT interval was checked 1 year later after a normal school day and it was 421 ms. Figure 4A shows the e.c.g. changes of a healthy 4-yr-old girl undergoing adenoidectomy with Althesin plus halothane anaesthesia. Preanaesthetic QT interval the presence of respiratory acidosis, hypoxia or other causes of sympathetic stimulation such as nervousness before operation (Apivor, 1960) or surgical manipulation (Alexander, 1971; Alexander, Bekheit and Fletcher, 1972). In the present study, the concentration of oxygen was 30% and end-tidal carbon dioxide was 5.5–6%. Surgical stimulation may be a factor. This is supported by Alexander (1971) who found that 23% of his patients developed ectopic rhythms in response to oral surgery under halothane anaesthesia. Alexander, Bekheit and Fletcher (1972) concluded that afferent impulses caused by oral surgery may be mediated by trigeminal nerve endings and may stimulate nerve centres in the medulla where sympathetic impulses reaching the heart are initiated.

The reason for the occurrence of BBB or BBB with aberrant conduction during halothane, but not enflurane, anaesthesia may be explained by the study of Atlee and Rusy (1977) who found that enflurane, like halothane (Atlee and Rusy, 1972), prolongs A–V nodal but not His–Purkinje and ventricular conduction. Atlee and Rusy (1977) suggested that re-entry of excitation requires slowing of conduction, unidirectional block and a pathway for an entrant impulse to reach the conduction system before arrival of the next normal impulse from above. This may explain why, in our study, and in the study of Alexander and Murtagh (1979), all the patients who developed aberrant conduction also had BBB.

Alexander (1971) suggested that the origin of aberration is supraventricular because lignocaine was relatively ineffective in abolishing this arrhythmia. In the present study, however, lignocaine abolished aberrant conduction with chaotic rhythm in three instances. Since the study reported here, lignocaine has proved to be ineffective in two of 10 children with aberrant conduction during halothane anaesthesia. In the present study, aberrant conduction led to bifocal ventricular tachycardia in a 9-yr-old boy. This arrhythmia might have been fatal without treatment; Gotta and others (1976) have found that aberrant conduction is a precursor of serious cardiac arrhythmia during halothane anaesthesia for oral surgery.

The frequency of BBB plus aberrant conduction after thiopentone induction was twice that after Althesin. The antiarrhythmic effect of Althesin was noted by Cundy (1973), Alexander (1974) and Saarnivaara and Kentala (1977).

QT interval in association with i.v. anaesthetics and suxamethonium

Prolongation of QT interval may be congenital (Jervell and Lange-Nielsen, 1957; Romano, Genme and Pongiglione, 1963; Ward, 1964) or acquired by administration of quinidine, tricyclic antidepressants (Schwartz and Wolf, 1978) or noradrenaline (Abildskov, 1976). Tricyclic antidepressants cause accumulation of noradrenaline at extracellular sites (Carlsson et al., 1969). Prolongation of QT during a hypertensive period has been found in patients with phaeochromocytoma (Cheng and Bashour, 1976). These results give further evidence that, in the presence of increased amounts of catecholamines, QT is prolonged. Hypocalcaemia may prolong QT (Surawicz, 1964). The children in the present study were healthy and in electrolyte balance.

QT interval was prolonged significantly after thiopentone induction and further after suxamethonium given after thiopentone, whereas it remained unchanged after Althesin. Suxamethonium given after Althesin did not prolong QT. Thiopentone depresses activity in all excitable tissues and increases the plasma concentration of catecholamines (Goodman and Gilman, 1975). Takki and others (1972) could not find an increase in the catecholamines in association with intubation after thiopentone plus suxamethonium. In the present study, the reason for prolongation of QT after thiopentone is unexplained. Stimulation of sympathetic ganglia may be caused by suxamethonium (Gallindo and Davis, 1962; Stoner and Urbach, 1968). Kadis and Gianelly (1973) found that thiopentone caused further aberration in patients with Wolf–Parkinson–White syndrome and Suppan (1979) has anaesthetized a patient with this disease using Althesin. Ahnve, Lundman and Shoaleh-var (1978) found that the prolongation of QT was a predictor of ventricular arrhythmia in acute myocardial infarction. Althesin may prevent ventricular arrhythmia or aberration by stabilizing the QT interval.

QT interval in association with QRS complex changes

The children with BBB without aberration had a normal preanaesthetic QT interval whereas, in those showing BBB with aberration, QT was significantly prolonged before anaesthesia and during the arrhythmia. One child with a preanaesthetic QT of 594 ms developed bifocal ventricular